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(54) Title: BISARYLCARBINOL CINNAMIC ACIDS AS INHIBITORS OF LEUKOTRIENE BIOSYNTHESIS

(57) Abstract

Compounds having the formula (I): $R^1R^2C(OR^3)\text{-}Ar^1\text{-}X\text{-}Ar^2\text{-}C(Ar^3){=}CHCO_2H$ are inhibitors of leukotriene biosynthesis. These compounds are useful as anti-asthmatic, anti-allergic, anti-inflammatory, and cytoprotective agents. They are also useful in treating angina, cerebral spasm, glomerular nephritis, hepatitis, endotoxemia, uveitis, and allograft rejection and in preventing the formation of atherosclerotic plaques.

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TITLE OF THE INVENTION

BISARYLCARBINOL CINNAMIC ACIDS AS INHIBITORS OF LEUKOTRIENE BIOSYNTHESIS

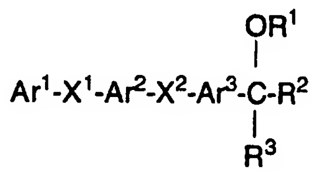
BACKGROUND OF THE INVENTION

The leukotrienes constitute a group of locally acting hormones, produced in living systems from arachidonic acid. The major leukotrienes are Leukotriene B_4 (abbreviated at LTB_4), LTC_4, LTD_4 and LTE_4. The biosynthesis of these leukotrienes begins with the action of the enzyme 5-lipoxygenase on arachidonic acid to produce the epoxide known as Leukotriene A_4 (LTA_4), which is converted to the other leukotrienes by subsequent enzymatic steps. Further details of the biosynthesis as well as the metabolism of the leukotrienes are to be found in the book *Leukotrienes and Lipoxygenases*, ed. J. Rokach, Elsevier, Amsterdam (**1989**). The actions of the leukotrienes in living systems and their contribution to various diseases states are also discussed in the book by Rokach.

European Patent Application 488,602(ICI) discloses compounds of structure 1 as inhibitors of 5-lipoxygenase. These compounds differ from the present invention most notably in the nature of X^1 of the reference structure which is defined as $-X_4-CR_2-$ or $-CR_2-X_4-$ whereas the present compounds have a carbon atom $[C(Ar^3)=CHCO_2H]$ to which is attached a carboxyl-carrying chain. EP 129,906 (Hoffmann-LaRoche) describes compounds such as 2 as intermediates with no disclosed biological activity and lacking the carbinol unit of the present compounds $[R^1R^2C(OR^3)-]$. Compounds of structure 3 are disclosed as lipoxygenase inhibitors in EP 196,184 and WO 90/01929 (Wellcome), differing from the present compounds in the nature of their X link and the substitution on their Ar unit. Compounds related to 4 are disclosed by Schrötter *et al.*, as having anti-infective/-anti-septic properties. There are structural differences from the present

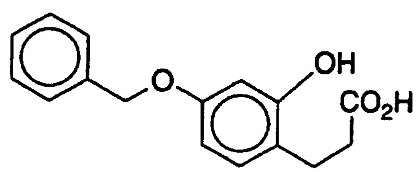
compounds, such as the absence of a carboxylic acid and the absence of the carbinol unit of the present compounds [$R^1R^2C(OR^3)$-].

1.



EP 488,602
ICI

2.



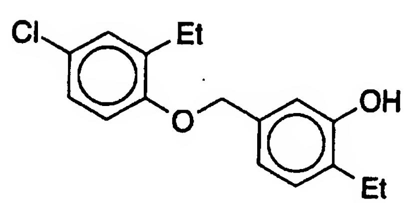
EP 129,906
Hoffmann-La Roche

3.

$$Ar - (L - Ar^1)_q - (X)k - (Y)_p - Q$$

EP 196,184
WO 90/01929
Wellcome

4.



Schrötter *et al.*
J. Prakt. Chem.,
1981, *323*, 129-132.

SUMMARY OF THE INVENTION

The present invention relates to compounds having activity as leukotriene biosynthesis inhibitors, to methods for their preparation,

and to methods and pharmaceutical formulations for using these compounds in mammals (especially humans).

Because of their activity as leukotriene biosynthesis inhibitors, the compounds of the present invention are useful as anti-asthmatic, anti-allergic, anti-inflammatory, and cytoprotective agents. They are also useful in treating angina, cerebral spasm, glomerular nephritis, hepatitis, endotoxemia, uveitis, and allograft rejection and in preventing the formation of atherosclerotic plaques.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds of the Formula I

$$R^1R^2C(OR^3)\text{-}Ar^1\text{-}X\text{-}Ar^2\text{-}C(Ar^3)\text{=}CHCO_2H$$

I

wherein:

Ar^1	is a 6-membered aromatic ring, containing 0-3N, substituted with one or two of the same or different R^4 groups;
Ar^2	is Ph(OH), substituted with one or two of the same or different R^5 groups;
Ar^3 and Ar^4	are independently a 5-membered aromatic ring containing one O or S and 0-3 N; a 5-membered aromatic ring containing 1-4 N; or a 6-membered aromatic ring containing 0-3 N; wherein said aromatic ring is substituted with one or two of the same or different R^6 groups;
X	is OCH_2, CH_2O, O, S, S(O) or $S(O)_2$;
R^1	is H, lower alkyl, lower perfluoroalkyl or Ar^4;
R^2	is H, lower alkyl or lower perfluoroalkyl;
R^3	is H or lower alkyl;
R^4 and R^5	are H, lower alkyl, lower alkoxy, lower alkythio, CN, CF_3, NO_2, CF_3O, or halogen;
R^6	is R^4, lower alkyl sulfinyl, lower alkylsulfonyl, or

$CO_2 R^7$;

R^7 is H, or lower alkyl

or a pharmaceutically acceptable salt thereof.

A preferred embodiment of the present invention provides compounds of Formula I wherein:

Ar^1 is	Phe or Pye, each of which is substituted with one or two of the same or different R^4 groups;
Ar^3 is	Ph, Py, Fu, Th, Tz, Im, or Pyr, each of which is substituted with one or two of the same or different R^6 groups;
X is	OCH_2, CH_2O, S, S(O), or $S(O)_2$;
R^1 is	H, lower alkyl, lower perfluoroalkyl, Ph, Py, Im, Fu or Tz;

and the remaining substitutents are as defined above in Formula I.

A more preferred embodiment of the present invention provides compounds of Formula I wherein:

Ar^1 is	Phe or Pye each of which is unsubstituted or substituted with halogen;
Ar^3 is	Ph, Py, Fu, Th, Tz, Im, or Pyr each of which is substituted with one or two of the same or different R^6 groups;
X is	OCH_2, CH_2O, S, S(O) or $S(O)_2$;
R^1 is	H, lower alkyl, lower perfluoroalkyl, Ph, Py or Tz;
R^6 is	R^4;

and the remaining substitutents are as defined above in Formula I.

Definitions

The following abbreviations have the indicated meanings:

Ac	=	acetyl
AIBN	=	2,2-azobisisobutyronitrile
Bn	=	benzyl
Bu_4NF	=	n-tetrabutylammonium fluoride
DMAP	=	4-(dimethylamino)pyridine

DMB	=	dimethoxybenzyl
DMF	=	N,N-dimethylformamide
DMSO	=	dimethyl sulfoxide
dppf	=	1,1'-bis(diphenylphosphino)ferrocene
Et3N	=	triethylamine
EtOAc	=	ethyl acetate
Fu	=	2- or 3-furyl
Im	=	1-, 2-, 4-, or 5-imidazolyl
KHMDS	=	potassium hexamethyldisilazane
LAH	=	lithium aluminum hydride
LDA	=	lithium diisopropylamide
mCPBA	=	meta-chloroperoxybenzoic acid
Ms	=	methanesulfonyl = mesyl
MsO	=	methanesulfonate = mesylate
NBS	=	N-bromosuccinimide
NCS	=	N-chlorosuccinimide
NIS	=	N-iodosuccinimide
NMP	=	N-methyl-2-pyrrolidinone
NSAID	=	non-steroidal anti-inflammatory drug
PCC	=	pyridinium chlorochromate
PDC	=	pyridinium dichromate
Ph	=	phenyl
Phe	=	benzenediyl
Py	=	2-, 3- or 4-pyridyl
Pye	=	pyridinediyl
Pyr	=	2- or 3-pyrrolyl
r.t.	=	room temperature
rac.	=	racemic
SEM	=	trimethylsilylethoxymethyl
TBDMS	=	tert-butyldimethylsilyl
TBDPS	=	tert-butyldiphenylsilyl
Tf	=	trifluoromethanesulfonyl = triflyl
TFAA	=	trifluoroacetic anhydride
TfO	=	trifluoromethanesulfonate = triflate

Th	=	2- or 3-thienyl
THF	=	tetrahydrofuran
TLC	=	thin layer chromatography
Ts	=	p-toluenesulfonyl = tosyl
TsO	=	p-toluenesulfonate = tosylate
Tz	=	2-, 4- or 5-thiazolyl

Alkyl group abbreviations

Me	=	methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl
c-Pr	=	cyclopropyl
c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

Alkyl means linear, branched and cyclic structures and combinations thereof.

"Lower alkyl" means alkyl groups of from 1 to 7 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s- and t-butyl, pentyl, hexyl, heptyl, cyclopropyl, cyclobutyl, cyclohexyl and the like.

"Lower perfluoro alkyl" includes lower alkyl groups in which all the hydrogen atoms are replaced by fluorine. Examples are $-CF_3$, $-CF_2CF_3$, c-Pr-F_5, c-Hex-F_{11} and the like.

"Lower alkoxy" means alkoxy groups of from 1 to 7 carbon atoms of a straight, branched, or cyclic configuration. Examples of lower alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like.

"Lower alkylthio" means alkylthio groups of from 1 to 7 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, etc. By way of illustration, the propylthio group signifies $-SCH_2CH_2CH_3$.

"Lower alkylsulfinyl" means those alkylsulfinyl groups of from 1 to 7 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkylsulfinyl groups are methyl-sulfinyl, 2-butylsulfinyl, cyclohexylmethylsulfinyl, etc. By way of illustration the 2-butylsulfinyl group signifies $-S(O)CH(CH_3)CH_2CH_3$.

"Lower alkylsulfonyl" means those alkylsulfonyl groups of from 1 to 7 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkylsulfonyl groups are methyl-sulfonyl, 2-butylsulfonyl, cyclohexylmethylsulfonyl, etc. By way of illustration the 2-butylsulfonyl group signifies $-S(O)_2CH(CH_3)CH_2CH_3$.

Halogen includes F, Cl, Br, and I.

Examples of "6-membered aromatic ring containing 0-3 N" include benzene, pyridine, pyridazine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine and 1,3,5-triazine.

Examples of "5-membered aromatic ring containing one O or S and 0-3N" include furan, oxazole, isoxazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, thiophene, thiazole, isothiazole, 1,2,5-thiadiazole and 1,3,4-thiadiazole.

Examples of "5-membered aromatic ring containing 1-4N" include pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole and tetrazole.

Optical Isomers - Diastereomers - Geometric Isomers

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Salts

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Utilities

The ability of the compounds of Formula I to inhibit biosynthesis of the leukotrienes makes them useful for preventing or reversing the symptoms induced by the leukotrienes in a human subject. This inhibition of the mammalian biosynthesis of leukotrienes indicates that the compounds and pharmaceutical compositions thereof are useful to treat, prevent, or ameliorate in mammals and especially in humans: 1) pulmonary disorders including diseases such as asthma, chronic bronchitis, and related obstructive airway diseases, 2) allergies and allergic reactions such as allergic rhinitis, contact dermatitis, allergic conjunctivitis, and the like, 3) inflammation such as arthritis or inflammatory bowel disease, 4) pain, 5) skin disorders such as atopic eczema, and the like, 6) cardiovascular disorders such as angina, formation of atherosclerotic plaques, myocardial ischemia, hypertension, platelet aggregation and the like, 7) renal insufficiency arising from ischaemia induced by immunological or chemical (cyclosporin) etiology and 8) migraine or cluster headache, 9) ocular conditions such as uveitis, 10) hepatitis resulting from chemical, immunological or infectious stimuli, 11) trauma or shock states such as burn injuries, endotoxemia and the like, 12) allograft rejection, 13) prevention of side effects associated with therapeutic administration of cytokines such as Interleukin II and tumor necrosis factor, 14) chronic lung diseases such as cystic fibrosis, bronchitis and other small- and large-airway diseases, 15) cholecystitis, 16) multiple sclerosis, and 17) proliferation of myoblastic leukemia cells.

Thus, the compounds of the present invention may also be used to treat or prevent mammalian (especially, human) disease states such as erosive gastritis; erosive esophagitis; diarrhea; cerebral spasm; premature labor; spontaneous abortion; dysmenorrhea; ischemia; noxious agent-induced damage or necrosis of hepatic, pancreatic, renal, or

myocardial tissue; liver parenchymal damage caused by hepatoxic agents such as CCl_4 and D-galactosamine; ischemic renal failure; disease-induced hepatic damage; bile salt induced pancreatic or gastric damage; trauma- or stress-induced cell damage; and glycerol-induced renal failure. The compounds also act as inhibitors of tumor metastasis and exhibit cytoprotective action.

The cytoprotective activity of a compound may be observed in both animals and man by noting the increased resistance of the gastrointestinal mucosa to the noxious effects of strong irritants, for example, the ulcerogenic effects of aspirin or indomethacin. In addition to lessening the effect of non-steroidal anti-inflammatory drugs on the gastrointestinal tract, animal studies show that cytoprotective compounds will prevent gastric lesions induced by oral administration of strong acids, strong bases, ethanol, hypertonic saline solutions, and the like.

Two assays can be used to measure cytoprotective ability. These assays are; (A) an ethanol-induced lesion assay and (B) an indomethacin-induced ulcer assay and are described in EP 140,684.

Dose Ranges

The magnitude of prophylactic or therapeutic dose of a compound of Formula I will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of Formula I and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general, the daily dose range for anti-asthmatic, anti-allergic or anti-inflammatory use and generally, uses other than cytoprotection, lie within the range of from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 10 mg per kg, and most preferably 0.1 to 1 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

For use where a composition for intravenous administration is employed, a suitable dosage range for anti-asthmatic, anti-inflammatory, or anti-allergic use is from about 0.001 mg to about 25 mg (preferably from 0.01 mg to about 1 mg) of a compound of Formula I per

kg of body weight per day and for cytoprotective use from about 0.1 mg to about 100 mg (preferably from about 1 mg to about 100 mg and more preferably from about 1 mg to about 10 mg) of a compound of Formula I per kg of body weight per day.

In the case where an oral composition is employed, a suitable dosage range for anti-asthmatic, anti-inflammatory or anti-allergic use is, e.g., from about 0.01 mg to about 100 mg of a compound of Formula I per kg of body weight per day, preferably from about 0.1 mg to about 10 mg per kg and for cytoprotective use from 0.1 mg to about 100 mg (preferably from about 1 mg to about 100 mg and more preferably from about 10 mg to about 100 mg) of a compound of Formula I per kg of body weight per day.

For the treatment of diseases of the eye, ophthalmic preparations for ocular administration comprising 0.001-1% by weight solutions or suspensions of the compounds of Formula I in an acceptable ophthalmic formulation may be used.

The exact amount of a compound of the Formula I to be used as a cytoprotective agent will depend on, *inter alia*, whether it is being administered to heal damaged cells or to avoid future damage, on the nature of the damaged cells (e.g., gastrointestinal ulcerations vs. nephrotic necrosis), and on the nature of the causative agent. An example of the use of a compound of the Formula I in avoiding future damage would be co-administration of a compound of the Formula I with an NSAID that might otherwise cause such damage (for example, indomethacin). For such use, the compound of Formula I is administered from 30 min. prior up to 30 minutes after administration of the NSAID. Preferably it is administered prior to or simultaneously with the NSAID, (for example, in a combination dosage form).

<u>Pharmaceutical Compositions</u>

Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed.

Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulisers. The compounds may also be delivered as powders which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound of Formula I in suitable propellants, such as fluorocarbons or hydrocarbons.

Suitable topical formulations of a compound of Formula I include transdermal devices, aerosols, creams, ointments, lotions, dusting powders, and the like.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral

or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of Formula I may also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719, the disclosures of which are hereby incorporated herein by reference.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed

tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 1 mg to about 500 mg of the active ingredient and each cachet or capsule contains from about 1 to about 500 mg of the active ingredient.

The following are examples of representative pharmaceutical dosage forms for the compounds of Formula I:

Injectable Suspension (I.M.)	mg/ml
Compound of Formula I	10
Methylcellulose	5.0
Tween 80	0.5
Benzyl alcohol	9.0
Benzalkonium chloride	1.0
Water for injection to a total volume of 1 ml	

Tablet	mg/tablet
Compound of Formula I	25
Microcrystalline Cellulose	415
Providone	14.0
Pregelatinized Starch	43.5
Magnesium Stearate	2.5
	500

Capsule	mg/capsule
Compound of Formula I	25
Lactose Powder	573.5
Magnesium Stearate	1.5
	600

Aerosol	Per canister
Compound of Formula I	24 mg
Lecithin, NF Liquid Concentrate	1.2 mg
Trichlorofluoromethane, NF	4.025 gm
Dichlorodifluoromethane, NF	12.15 gm

Combinations with Other Drugs

In addition to the compounds of Formula I, the pharmaceutical compositions of the present invention can also contain other active ingredients, such as cyclooxygenase inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), peripheral analgesic agents such as zomepirac diflunisal and the like. The weight ratio of the compound of the Formula I to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the Formula I is combined with an NSAID the weight ratio of the compound of the Formula I to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the Formula I and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

NSAIDs can be characterized into five groups:

(1) propionic acid derivatives;

(2) acetic acid derivatives;

(3) fenamic acid derivatives;

(4) oxicams; and

(5) biphenylcarboxylic acid derivatives,
or a pharmaceutically acceptable salt thereof.

The propionic acid derivatives which may be used comprise: alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, prano-profen, suprofen, tiaprofenic acid, and tioxaprofen. Structurally related propionic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be included in this group.

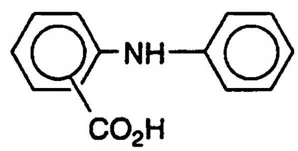
Thus, "propionic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free $-CH(CH_3)COOH$ or $-CH_2CH_2COOH$ group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g., $-CH(CH_3)COO^-Na^+$ or $-CH_2CH_2COO^-Na^+$), typically attached directly or via a carbonyl function to a ring system, preferably to an aromatic ring system.

The acetic acid derivatives which may be used comprise: indomethacin, which is a preferred NSAID, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac. Structually related acetic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

Thus, "acetic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free $-CH_2COOH$ group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g., $-CH_2COO^-Na^+$), typically attached directly to a ring system, preferably to an aromatic or heteroaromatic ring system.

The fenamic acid derivatives which may be used comprise: flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid. Structurally related fenamic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

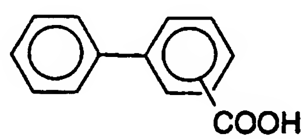
Thus, "fenamic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic structure:



which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g., $-COO^{-}Na^{+}$.

The biphenylcarboxylic acid derivatives which can be used comprise: diflunisal and flufenisal. Structurally related biphenylcarboxylic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

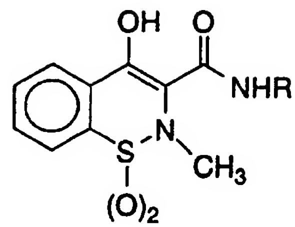
Thus, "biphenylcarboxylic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic structure:



which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g., $-COO^{-}Na^{+}$.

The oxicams which can be used in the present invention comprise: isoxicam, piroxicam, sudoxicam and tenoxican. Structurally related oxicams having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

Thus, "oxicams" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which have the general formula:



wherein R is an aryl or heteroaryl ring system.

The following NSAIDs may also be used: amfenac sodium, aminoprofen, anitrazafen, antrafenine, auranofin, bendazac lysinate, benzydanine, beprozin, broperamole, bufezolac, cinmetacin, ciproquazone, cloximate, dazidamine, deboxamet, delmetacin, detomidine, dexindoprofen, diacerein, di-fisalamine, difenpyramide, emorfazone, enfenamic acid, enolicam, epirizole, etersalate, etodolac, etofenamate, fanetizole mesylate, fenclorac, fendosal, fenflumizole, feprazone, floctafenine, flunixin, flunoxaprofen, fluproquazone, fopirtoline, fosfosal, furcloprofen, glucametacin, guaimesal, ibuproxam, isofezolac, isonixim, isoprofen, isoxicam, lefetamine HCl, leflunomide, lofemizole, lonazolac calcium, lotifazole, loxoprofen, lysin clonixinate, meclofenamate sodium, meseclazone, nabumetone, nictindole, nimesulide, orpanoxin, oxametacin, oxapadol, perisoxal citrate, pimeprofen, pimetacin, piproxen, pirazolac, pirfenidone, proglumetacin maleate, proquazone, pyridoxiprofen, sudoxicam, talmetacin, talniflumate, tenoxicam, thiazolinobutazone, thielavin B, tiaramide HCl, tiflamizole, timegadine, tolpadol, tryptamid, and ufenamate.

The following NSAIDs, designated by company code number (see e.g., Pharmaprojects), may also be used: 480156S, AA861, AD1590, AFP802, AFP860, AI77B, AP504, AU8001, BPPC, BW540C, CHINOIN 127, CN100, EB382, EL508, F1044, GV3658, ITF182, KCNTEI6090, KME4, LA2851, MR714, MR897, MY309, ONO3144, PR823, PV102, PV108, R830, RS2131, SCR152, SH440, SIR133, SPAS510, SQ27239, ST281, SY6001, TA60, TAI-901 (4-benzoyl-1-indancarboxylic acid), TVX2706, U60257, UR2301, and WY41770.

Finally, NSAIDs which may also be used include the salicylates, specifically acetyl salicylic acid and the phenylbutazones, and pharmaceutically acceptable salts thereof.

In addition to indomethacin, other preferred NSAIDs are acetyl salicylic acid, diclofenac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, naproxen, phenylbutazone, piroxicam, sulindac, and tolmetin. Pharmaceutical compositions comprising the Formula I compounds may also contain inhibitors of the biosynthesis of the leukotrienes such as are disclosed in EP 138,481 (April 24,1985), EP 115,394 (August 8, 1984), EP 136,893 (April 10, 1985), and EP 140,709 (May 8, 1985), which are hereby incorporated herein by reference.

The compounds of the Formula I may also be used in combination with leukotriene antagonists such as those disclosed in EP 106,565 (April 25, 1984) and EP 104,885 (April 4, 1984) which are hereby incorporated herein by reference and others known in the art such as those disclosed in EP Application Nos. 56,172 (July 21, 1982) and 61,800 (June 10, 1982); and in U.K. Patent Specification No. 2,058,785 (April 15, 1981), which are hereby incorporated herein by reference.

Pharmaceutical compositions comprising the Formula I compounds may also contain as the second active ingredient, prostaglandin antagonists such as those disclosed in EP 11,067 (May 28, 1980) or thromboxane antagonists such as those disclosed in U.S. Pat. 4,237,160. They may also contain histidine decarboxylase inhibitors such as α-fluoromethylhistidine, described in U.S. Pat. 4,325,961. The compounds of the Formula I may also be advantageously combined with an H_1 or H_2-receptor antagonist, such as for instance acetamazole, aminothiadiazoles disclosed in EP 40,696 (December 2, 1981), benadryl, cimetidine, famotidine, framamine, histadyl, phenergan, ranitidine, terfenadine and like compounds, such as those disclosed in U.S. Patent Nos. 4,283,408; 4,362,736; and 4,394,508. The pharmaceutical compositions may also contain a K^+/H^+ ATPase inhibitor such as omeprazole, disclosed in U.S. Pat. 4,255,431, and the like. Compounds of Formula I may also be usefully combined with most cell stabilizing agents, such as 1,3-bis(2-carboxychromon-5-yloxy)-2-

hydroxypropane and related compounds described in British Patent Specifications 1,144,905 and 1,144,906. Another useful pharmaceutical composition comprises the Formula I compounds in combination with serotonin antagonists such as methysergide, the serotonin antagonists described in *Nature, 316*, 126-131 **(1985)**, and the like. Each of the references referred to in this paragraph is hereby incorporated herein by reference.

Other advantageous pharmaceutical compositions comprise the Formula I compounds in combination with anti-cholinergics such as ipratropium bromide, bronchodilators such as the beta agonist salbutamol, metaproterenol, terbutaline, fenoterol and the like, and the anti-asthmatic drugs theophylline, choline theophyllinate and enprofylline, the calcium antagonists nifedipine, diltiazem, nitrendipine, verapamil, nimodipine, felodipine, etc., and the corticosteroids, hydrocortisone, methylprednisolone, betamethasone, dexamethasone, beclomethasone, and the like.

Methods of Synthesis

Compounds of the present invention can be prepared according to the following methods.

Compounds of Formula I of the present invention may be prepared according to the synthetic routes outlined in Scheme 1 to 3 and by the following methods described herein.

Scheme 1

Compounds of Formula 1A and 1B can be synthesized using the route described in Scheme 1. Bromophenol II can be acetylated by treating a mixture of II and acetyl chloride in the presence of a base such as pyridine in a solvent such as dichloromethane to yield the corresponding acetate which, upon heating neat with a Lewis acid such as aluminum chloride, gives the acyl derivative III. Reaction of III with first an inorganic base such as sodium hydride in an organic solvent such as benzene followed by addition of a carbonate such as diethylcarbonate furnishes the intermediate IV. The intermediate IV is then transformed

using trifluoromethanesulfonic anhydride, in the presence of an amine such as triethylamine, in a neutral solvent such as dichloromethane, to the corresponding triflate V. Cross coupling of this material with an aryl lithium species resulting from reaction of an aryl halide (Br or I) with an alkyl lithium such as n-BuLi in a mixture of THF/hexanes, in the presence of trimethyl borate and catalyzed by a Pd(0) species such as $(Ph_3P)_4Pd$, in a mixture of THF/water as solvent, affords derivatives VI. Compounds of Formula VIII can be obtained by heating a mixture of VI and a thiophenol of general structure VII (Scheme 5) in a polar solvent such as N-methyl-2-pyrrolidinone with an inorganic base like potassium carbonate. Compounds of Formula 1A can be obtained by an hydrolysis of compounds VIII using a base such as aqueous sodium hydroxide in a hot organic solvant such as THF.

Compounds of Formula 1B can be obtained by treating compounds of general structure VIII in the presence of a peracid such as mCPBA in an organic solvent such as dichloromethane, followed by a basic hydrolysis similar to the transformation of compounds VIII to IA.

Scheme 2

Compounds of Formula 1C can be synthesized using the route described in Scheme 2. The meta-cresol X is converted in several steps to the compound XI using the same protocol as described in Scheme 1 for the conversion of II to VI. Intermediate XI is then brominated by heating in the presence of a brominating reagent such as NBS in an organic solvent such as carbon tetrachloride in the presence of a catalytic amount of a radical initiator such as AIBN, giving access to compounds XII. Bromide displacement can be accomplished using a phenol of a general structure XIII (Scheme 4) in the presence of an inorganic base such as cesium carbonate in an aprotic dipolar solvent such as DMF to afford compounds XIV which upon basic hydrolysis similar to the conversion of compound VIII to IA (Scheme 1) gives compound 1C.

Scheme 3

Compounds of Formula 1D can be prepared as shown in Scheme 3. The aromatic bromide VI can be reacted by heating in the presence of trimethylsilylethane thiol and an inorganic base such as potassium carbonate in a polar solvent such as N-methyl-2-pyrroli-dinone to afford derivative XV. The thiol derivatives XVI can be obtained by treating XV with Bu4NF in an organic solvent such as DMF. Sulfur linked compounds may be obtained by heating thiol XVI with an aromatic bromide of general Formula XVII (Scheme 6) in the presence of an inorganic base such as potassium carbonate in a polar solvent such as N-methyl-2-pyrrolidinone to yield compounds of Formula XVIII which upon basic hydrolysis similar to the conversion of compounds VIII to IA (Scheme 1) gives compound ID.

<u>Scheme 4</u>

The phenols of structure XIII can be obtained following the route described in Scheme 4. The protected bromophenol XIX can be transformed to the tertiary alcohol XX by first a transmetallation using magnesium in an organic solvent such as THF or by using an alkyl-lithium such as n-butyllithium followed by an addition of the appropriate ketone. Alternatively fluoroketone XXII can be transformed to the corresponding benzyl ether XXIII by treating with the benzyloxy sodium salt in an organic solvent such as DMF. Treatment of compound XXIII with alkyl lithium such as methyl lithium or with a Grignard reagent such as methyl magnesium bromide provides compound XX. The tertiary alcohol XX can be alkylated to XXI with an alkyl halide such as methyl iodide in the presence of base such as potassium hydride in an organic solvent such as DMF. Removal of the protecting group by treating XX or XXI with hydrogen in the presence of a catalyst such as Pd/C (P = Bn or 3,4-DMB) or by using a fluoride source such as tetrabutylammonium fluoride in an organic solvent such as THF (P = TBDMS or TBDPS) provides the phenols of structure XIII.

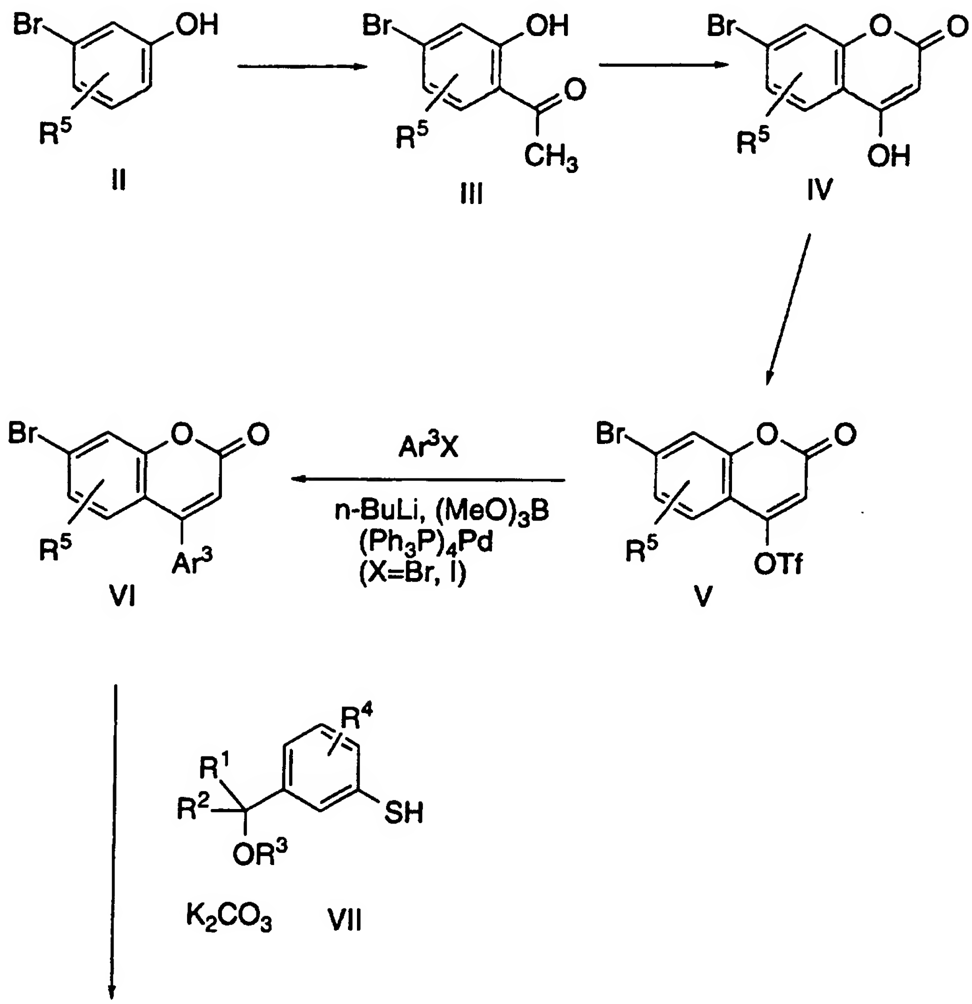
<u>Scheme 5</u>

The thiophenols of the general Formula VII can be obtained using a multi-step sequence shown in Scheme 5. The bromofluorobenzene XXIV can be first transmetallated with magnesium in an organic solvent such as THF followed by the addition of the appropriate ketone to obtain the corresponding tertiary alcohol of the general Formula XXV. The introduction of the thiol function can be effected by treating the fluoro derivatives XXV with a thiol source such as trimethylsilylethane thiol in the presence of an hydride such as sodium hydride in an aprotic solvent such as DMF. The resulting compound XXVI can be converted to the thiol VII by treatment with a fluoride source such as tetrabutylammonium fluoride in an organic solvent such as THF. Alternatively, thiol VII can be obtained by treating the fluoroketone XXVIII with sodium methylthiolate giving XXIX and followed by treating XXIX with the appropriate Grignard reagent to provide XXX. Then cleavage of the methylthio ether group can be effected by first oxidizing the sulfur to the sulfoxide using an oxidizing reagent such as mCPBA and then by treating it with trifluoroacetic anhydride to give thiol VII. The tertiary alcohol XXX can be alkylated to XXXI with an alkyl halide such as methyl iodide in the presence of base such as potassium hydride in an organic solvant such as DMF followed by a similar deprotection as described for XXX to VII.

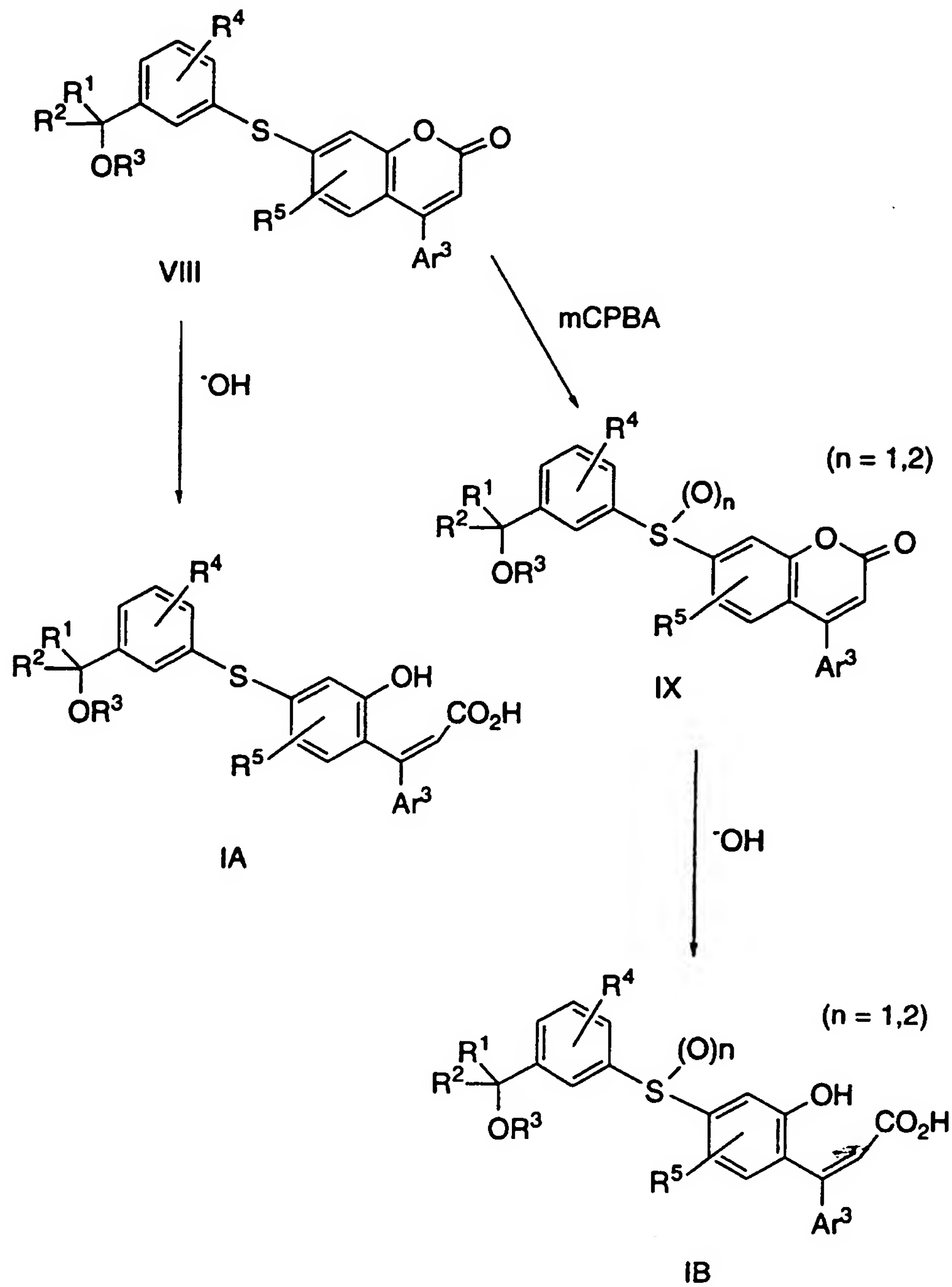
Scheme 6

The bromopyridines of the general Formula XVII can be obtained starting with the 2,6-dibromopyridine and using the same protocol as described for the transformation of compound XIX to XX in Scheme 4.

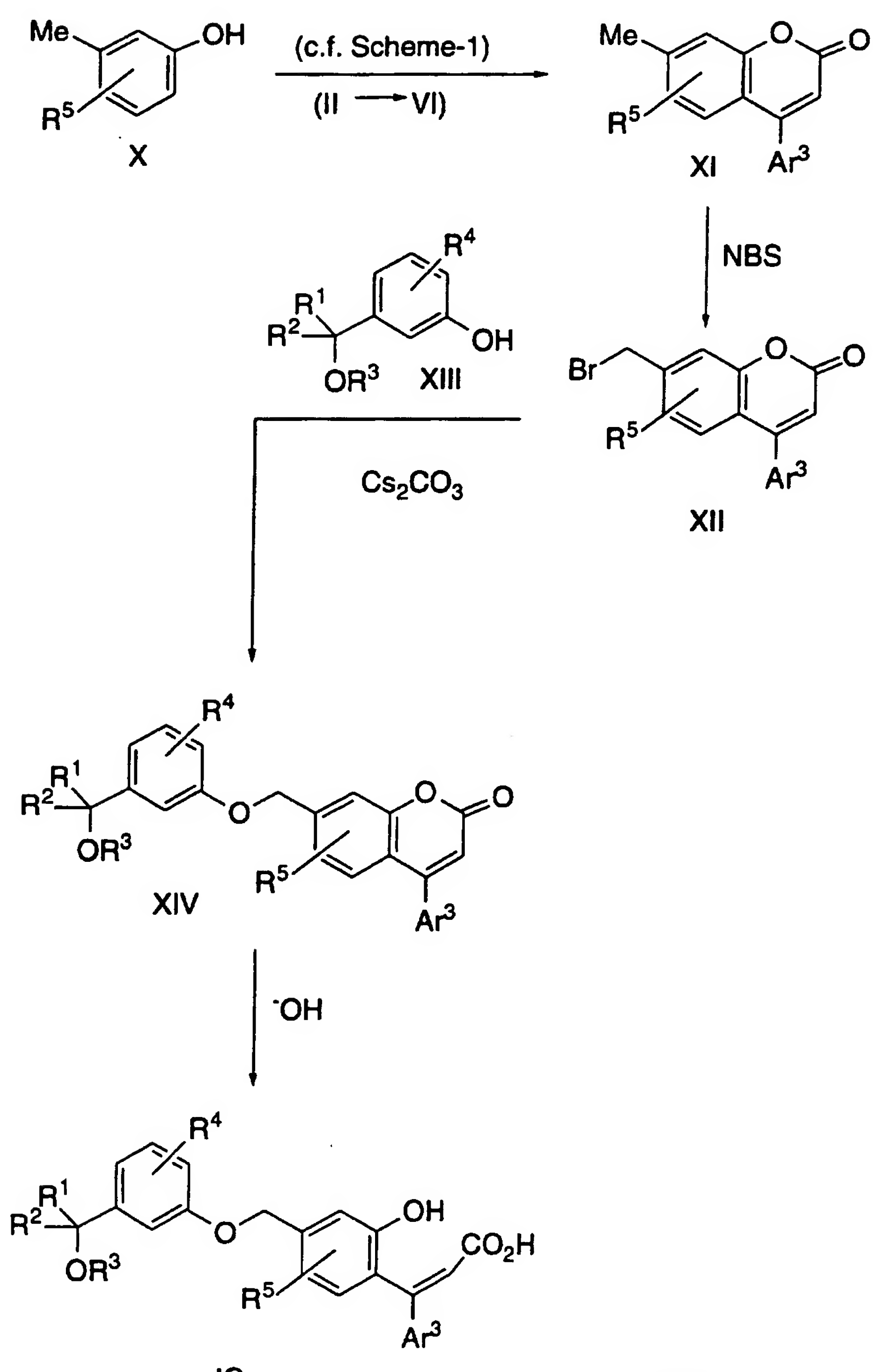
SCHEME 1



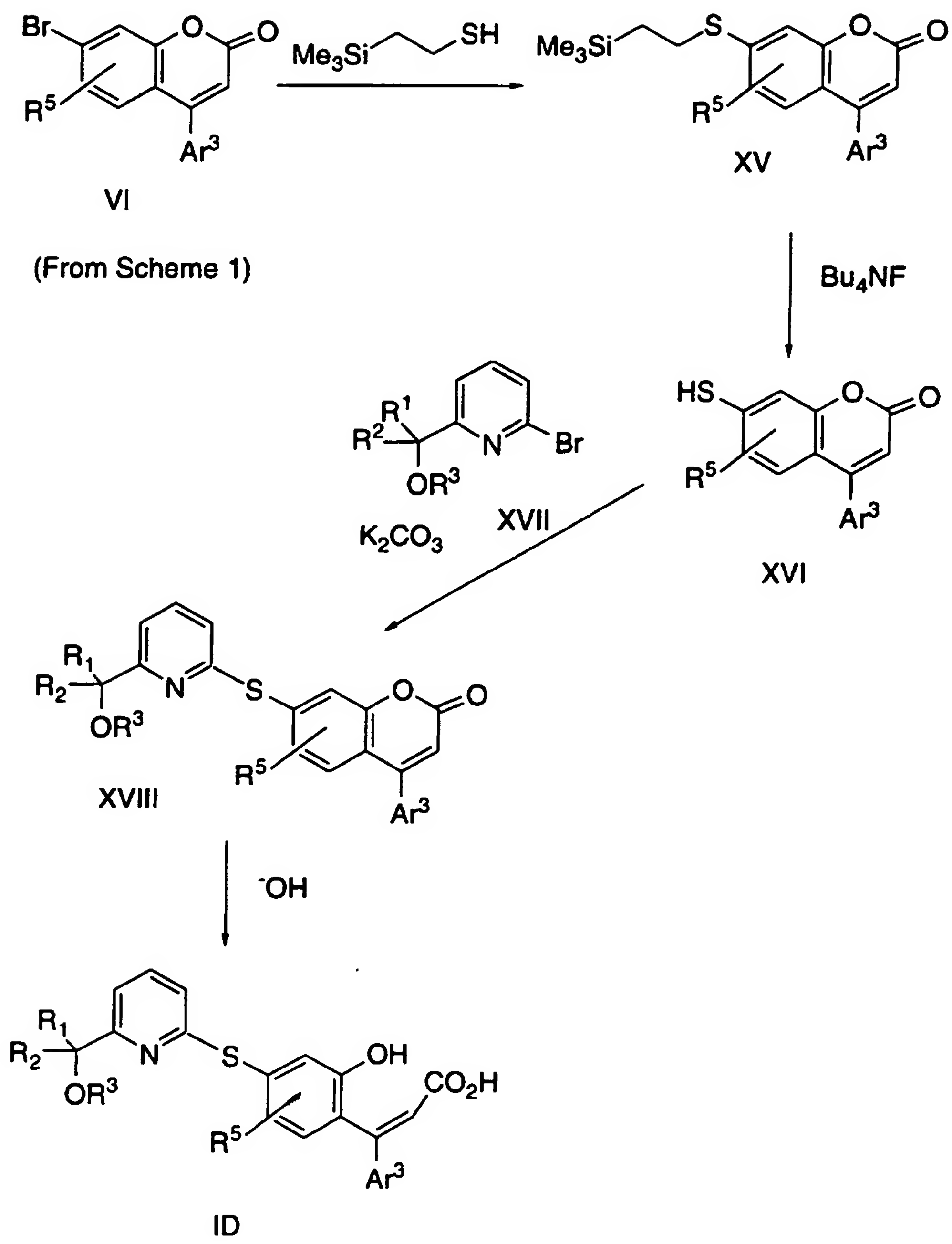
SCHEME 1 (CONT'D)



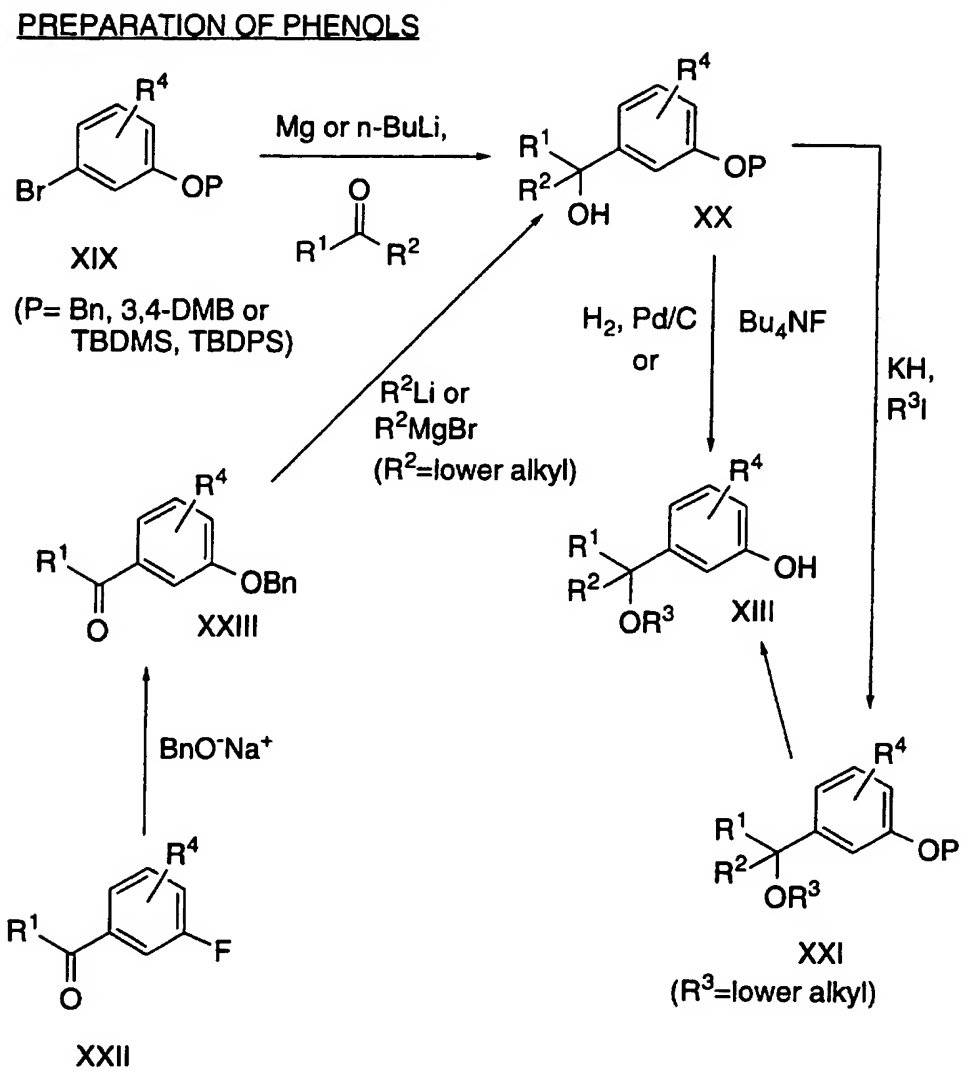
SCHEME 2


Me
OH
R5
X
(c.f. Scheme-1)
(II → VI)
Me
O
O
R5
XI
Ar3
NBS
R4
R1
R2
OH
OR3
XIII
Br
O
O
R5
Ar3
XII
Cs2CO3
R4
R1
R2
O
O
O
OR3
XIV
R5
Ar3
-OH
R4
R1
R2
O
OH
CO2H
OR3
R5
Ar3
IC

SCHEME 3

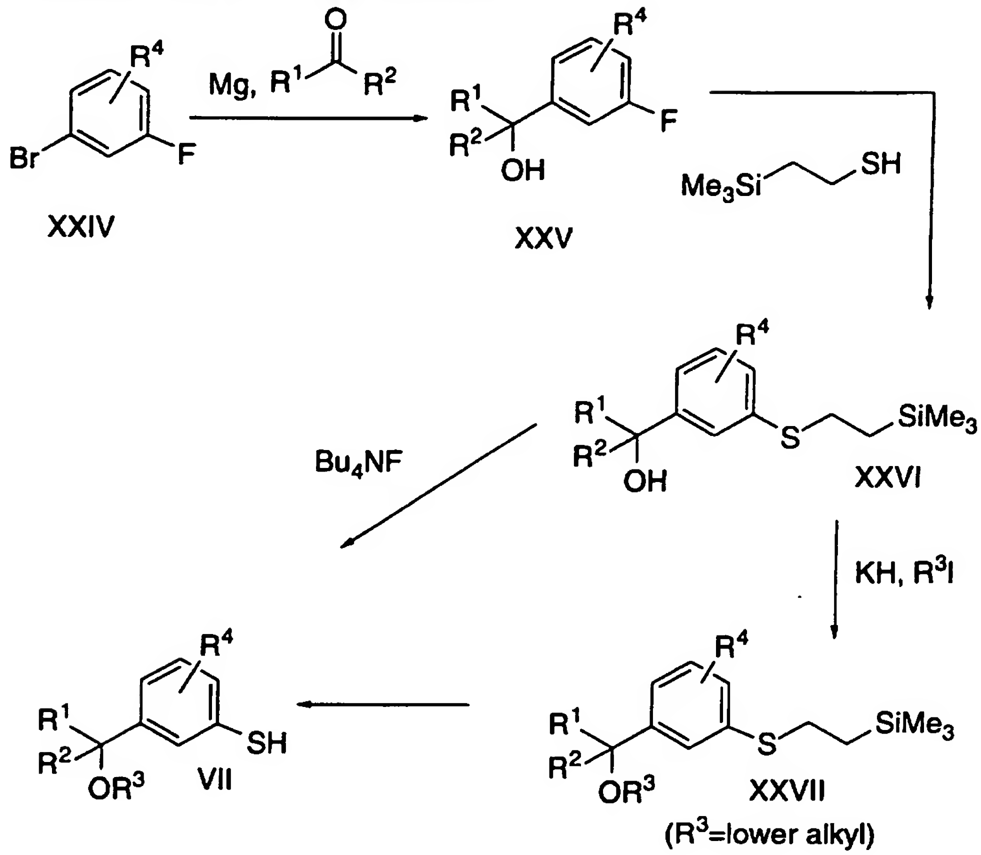

Br
O
O
R5
Ar3
VI
(From Scheme 1)
Me3Si
SH
Me3Si
S
XV
Bu4NF
HS
XVI
R1
R2
OR3
N
Br
K2CO3
XVII
XVIII
-OH
OH
CO2H
ID

SCHEME 4

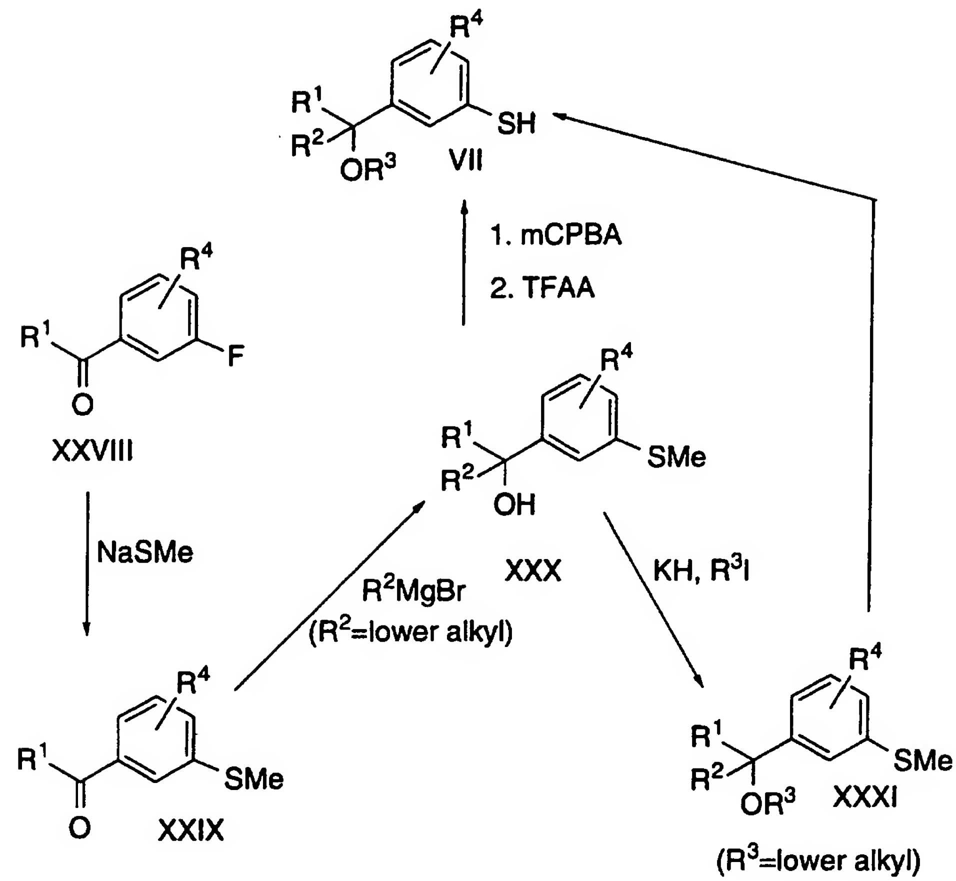

PREPARATION OF PHENOLS
R4
Br
OP
XIX
(P= Bn, 3,4-DMB or TBDMS, TBDPS)
Mg or n-BuLi,
O
R1
R2
OH
XX
H2, Pd/C or
Bu4NF
KH, R3I
R2Li or R2MgBr (R2=lower alkyl)
OBn
XXIII
OH
OR3
XIII
BnO-Na+
F
XXII
XXI
(R3=lower alkyl)

SCHEME 5

PREPARATION OF THIOPHENOLS

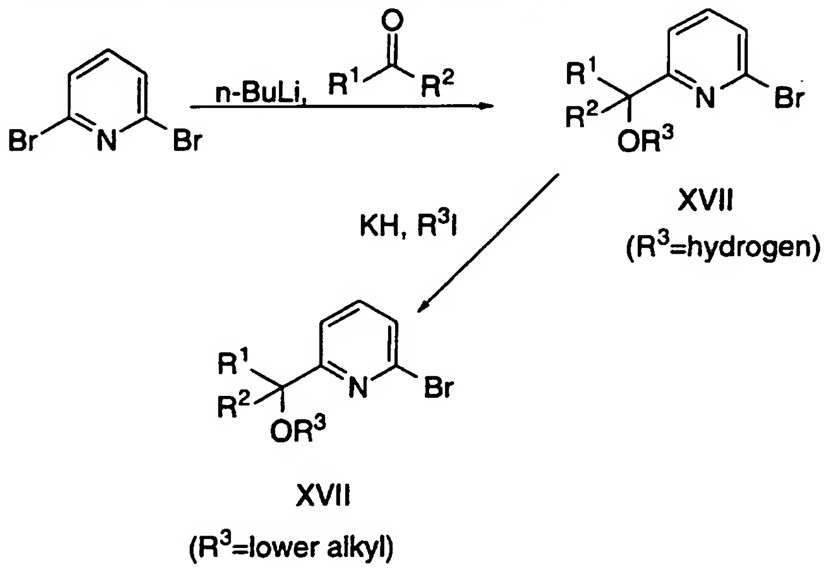


SCHEME 5 (CONT'D)



SCHEME 6

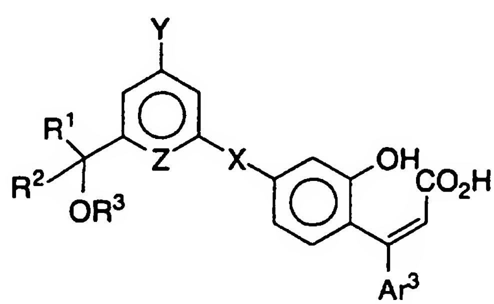
PREPARATION OF BROMOPYRIDINES



Representative Compounds

Table I illustrates compounds of Formula Ia, which are representative of the present invention.

TABLE I



Ia

EX	R^1	R^2	R^3	Z	Y	X	Ar^3
1	Et	Et	H	CH	F	OCH_2	3-Fu
2	Et	Et	H	CH	F	S	3-Fu
3	CF_3	CF_3	H	CH	F	S	3-Fu
4	CF_3	CF_3	H	CH	F	S	4-F-Ph
5	CF_3	CF_3	H	CH	F	S	3-Py
6	CF_3	CF_3	H	CH	F	S	5-Tz
7	CF_3	CF_3	H	CH	F	S	4-Tz
8	CF_3	CF_3	H	CH	F	S	4-Py
9	CF_3	CF_3	H	CH	F	OCH_2	4-F-Ph
10	CF_3	CF_3	H	N	H	S	3-Fu
11	n-Bu	H	H	CH	F	OCH_2	4-F-Ph
12	CF_3	CF_3	H	CH	F	$S(O)_2$	4-F-Ph
13	CF_3	CF_3	H	CH	F	S(O)	4-F-Ph
14	CF_3	CF_3	H	CH	F	S	4-Cl-Ph
15	CF_3	CF_3	H	CH	F	S	2,4-Cl-Ph
16	CF_3	CF_3	H	N	H	S	4-F-Ph
17	CF_3	CF_3	H	CH	F	S	2-Py
18	CF_3	CF_3	H	CH	F	S	3-N-MePyr
19	CF_3	CF_3	H	CH	F	S	Ph
20	CF_3	CF_3	H	CH	F	S	1-Im
21	Ph	CF_3	H	CH	F	S	3-Fu
22	2-Tz	CF_3	H	CH	F	S	4-F-Ph
23	Ph	Et	H	CH	F	S	3-Fu
24	2-Tz	Me	H	CH	F	S	3-Fu
25	2-Tz	iPr	H	CH	F	S	3-Fu
26	2-Im	Et	H	CH	F	OCH_2	3-Fu
27	2-Py	Et	H	CH	H	OCH_2	3-Fu
28	2-Tz	Et	H	CH	F	OCH_2	3-Th
29	2-Tz	Et	H	CH	F	OCH_2	3-Fu
30	2-Tz	Et	H	CH	F	OCH_2	4-F-Ph
31	2-Tz	Et	H	CH	F	$S(O)_2$	3-Fu
32	2-Tz	Et	H	CH	F	S	3-(5-Cl-Th)
EX	R^1	R^2	R^3	Z	Y	X	Ar^3

33	2-Tz	Et	H	CH	F	S	3-Th
34	2-Tz	Et	H	CH	F	S	Ph
35	2-Tz	Et	H	CH	F	S	3-Fu
36	2-Tz	Et	H	CH	F	S	4-F-Ph
37	2-Tz	Et	H	CH	H	OCH_2	3-Fu
38	2-Tz	Et	H	CH	H	OCH_2	3-Th
39	CF_3	CF_3	H	CH	F	S	3-NO_2-Ph
40	CF_3	CF_3	H	CH	F	S	3-Cl,4-F-Ph
41	CF_3CF_2	CF_3CF_2	H	CH	F	S	4-F-Ph
42	CF_3	CF_3	H	CH	F	S	CF_3
43	CF_3	CF_3	H	CH	F	S	3-CF_3O-Ph
44	CF_3	CF_3	CH_3	CH	F	S	3-Fu
45	CF_3	CF_3	CH_3	CH	F	S	4-F-Ph

Assays for Determining Biological Activity

Compounds of Formula I can be tested using the following assays to determine their mammalian leukotriene biosynthesis inhibiting activity.

Human 5-lipoxygenase inhibitor screen

Objective of the Assay: The objective of the assay is to select agents which specifically inhibit the activity of human 5-lipoxygenase using a 100,000 x g supernatant fraction prepared from insect cells infected with recombinant baculovirus containing the coding sequence for human 5-lipoxygenase. Enzyme activity is measured spectrophotometrically from the optimal rate of conjugated diene formation (A_{234}) measured after the incubation of the enzyme with arachidonic acid in the presence of ATP, calcium ions and phosphatidylcholine.

Description of Procedure: The activity of 5-lipoxygenase is measured using a spectrophotometric assay and recombinant human 5-lipoxygenase as a source of enzyme. The 100,000 x g fraction from S19 cells infected with the recombinant baculovirus rvH5LO(8-1) containing the coding region sequence for human 5-lipoxygenase is prepared as

described by Denis *et al.*, (*J. Biol. Chem.*, *266*, 5072-5079 (**1991**)). The enzymatic activity is measured, using a spectrophoto-metric assay from the optimal rate of conjugated diene formation (A234) using the procedure described by Riendeau *et al.*, (*Biochem. Pharmacol.*, *38*, 2323-2321, (**1989**)) with minor modifications. The incubation mixture contains 50 mM sodium phosphate pH 7.4, 0.2 mM ATP, 0.2 mM $CaCl_2$, 20 µM arachidonic acid (5 µL from a 100-fold concentrated solution in ethanol), 12 µg/mL phosphatidylcholine, an aliquot of the 100,000 x g fraction (2-10 µL) and inhibitor (0.5 mL final volume). Inhibitors are added as 500-fold concentrated solutions in DMSO. Reactions are initiated by the addition of an aliquot of the enzyme preparation and the rate of conjugated diene formation is followed for 2 min. at r.t. The reactions are performed in semi-micro cuvettes (0.7 mL capacity, 10 mm path length and 4 mm internal width) and the absorbance changes are recorded with a Hewlett-Packard diode array spectrophotometer (HP 8452A) connected to the ChemStation using UV/VIS Kinetics Software. Enzymatic activity is calculated from the optimal rate of the reaction by a linear fit of the variation of A_{234} during the first twenty seconds using the least square method for the equation $A_{234}=V_ot + A°$ where V_o is the rate, t is the time, and A_o is the absorbance at zero time. The results are expressed as percentages of inhibition of the reaction rate relative to controls (typically between 0.15-0.21 AU/min) containing the DMSO vehicle.

Human Polymorphonuclear (PMN) Leukocyte LTB_4 Assay

A. Preparation of Human PMN

Human blood is obtained by antecubital venepuncture from consenting volunteers who have not taken medication within the previous 7 days. The blood is immediately added to 10% (v/v) trisodium citrate (0.13 M) or 5% (v/v) sodium heparin (1000 IU/mL). PMNs are isolated from anticoagulated blood by dextran sedimentation of erythrocytes followed by centrifugation through Ficoll-Hypaque (specific gravity 1.077), as described by Boyum (*Scand. J. Clin. Lab. Invest.*, *21* (Supp 97), 77 (**1968**)). Contaminating erythrocytes are removed by lysis

following exposure to ammonium chloride (0.16 M) in Tris buffer (pH 7.65), and the PMNs are resuspended at 5 x 10^5 cells/mL in HEPES (15 mM)-buffered Hanks balanced salt solution containing Ca^{2+} (1.4 mM) and Mg^{2+} (0.7 mM), pH 7.4.

B. Generation and Radioimmunoassay of LTB_4

PMNs (0.5 mL; 2.5 x 10^5 cells) are placed in plastic tubes and incubated (37°C, 2 min) with test compounds at the desired concentration or vehicle (DMSO, final concentration 0.2%) as control. The synthesis of LTB_4 is initiated by the addition of calcium ionophore A23187 (final concentration 10 µM) or vehicle in control samples and allowed to proceed for 5 min. at 37°C. The reactions are then terminated by the addition of cold methanol (0.25 mL) and samples of the entire PMN reaction mixture are removed for radioimmunoassay of LTB_4.

Samples (50 µL) of authentic LTB_4 of known concentration in radioimmunoassay buffer (RIA) buffer (potassium phosphate 1 mM; disodium EDTA 0.1 mM; Thimerosal 0.025 mM; gelatin 0.1%, pH 7.3) or PMN reaction mixture diluted 1:1 with RIA buffer are added to reaction tubes. Thereafter [^{3}H]-LTB_4 (10 nCi in 100 µL RIA buffer) and LTB_4-antiserum (100 µL of a 1:3000 dilution in RIA buffer) are added and the tubes vortexed. Reactants are allowed to equilibrate by incubation overnight at 4°C. To separate antibody-bound from free LTB_4, aliquots (50 µL) of activated charcoal (3% activated charcoal in RIA buffer containing 0.25% Dextran T-70) are added, the tubes vortexed, and allowed to stand at r.t. for 10 min. prior to centrifugation (1500 x g; 10 min; 4°C). The supernatants containing antibody-bound LTB_4 are decanted into vials and Aquasol 2 (4 mL) is added. Radioactivity is quantified by liquid scintillation spectrometry. The specificity of the antiserum and the sensitivity of the procedure have been described by Rokach *et al.*, *Prostaglandins Leukotrienes and Medicine*, *13*, 21 (**1984**). The amount of LTB_4 produced in test and control samples is calculated. Inhibitory dose-response curves are constructed using a four-parameter algorithm and from these the IC_{50} values are determined.

Human Whole Blood Assay IN VITRO for LTB_4 Production

Fresh blood is collected in heparinized tubes by venipuncture from human volunteers. A 500 mL aliquot is incubated with one of the test compounds at final concentrations varying from 3 nM to 3 mM at 37°C for 15 min. Drug stock solutions are made up in DMSO and 1 µL of the stock solution is added to each assay tube. The blood is then incubated with A23187 (in 5 µL autologous plasma, 25 µM final concentration) at 37°C for 30 min. At the end of incubation, plasma is obtained (12,000 x g, 15 min) and a 100 µL aliquot is added to 400 µL methanol for protein precipitation. The mixture is vortexed, centrifuged and the supernatant stored at -70°C until assayed for LTB_4 by standard RIA.

Pulmonary Mechanics in Trained Conscious Squirrel Monkeys - A Non-Invasive Technique

Objective of the Assay: To assess pulmonary mechanics changes in the airways of conscious squirrel monkeys with the use of a double plethysmograph instead of thoracic catheterization of the pleural space as in the former invasive technique to measure airway resistance (R_L) and dynamic compliance (C_{dyn}). The non-invasive technique measures changes in the pulmonary parameter "specific airway resistance" (sRaw) which is defined as airway resistance x thoracic gas volume. Agonists like LTD_4, 50 µg/mL or Ascaris suum antigen (1:25 dilution) aerosol challenge cause an increase in sRaw values, i.e., bronchoconstriction, and consequently allow the evaluation of specific antagonists against these agonists.

For evaluation of compounds in this model, monkeys are fasted overnight and dosed the following morning. The compound is dissolved in 1% methocel solution and given orally at doses ranging from 1 to 0.003 mg/kg in a volume of 1 mL/kg in the home cage. Three h later the monkeys are placed in a chair within a thoracic plethysmograph whilst the muzzle of the monkey is placed into a nasal plethysmograph through which he breathes. Baseline values for sRaw (cm H_2O x sec.) are taken and at 4 h post compound administration, the monkeys are challenged with an aerosol of the specific agonist. The aerosol is generated by an ultrasonic DeVilbiss nebulizer and administered to the

monkeys in the nasal plethysmograph at a rate of 2 litres/minute with the aid of a Pulmo-Aide pump (DeVilbiss, 561 series) for 10 min. For data collection, a Buxco Electronics Inc. respiratory computer is utilized which facilitates continuous recording of pulmonary function changes and derives a value for sRaw for each animal.

Following challenge, each minute of data is calculated as a percent change from control values for specific airway resistance (sRaw). The results for each test compound are subsequently obtained for a minimum period of 60 minutes post challenge which are then compared to previously obtained historical baseline control values for that monkey. In addition, the overall values for 60 minutes post-challenge for each monkey (historical baseline values and test values) are averaged separately and are used to calculate the overall percent inhibition of LTD4 or <u>Ascaris</u> antigen response by the test compound. For statistical analysis, paired t-test is used (Reference: Pennock, B.E. *et al.*, *J. Appl. Physiol.*: *Respirat. Environ. Exercise Physiol.*, *46* (2) 399-406, **1979**.

<u>DOG MODEL</u>

<u>Whole Blood *(ex vivo)* LTB4 and Urinary LTE4 Excretion Assays</u>

Normal male dogs are anaesthetised, bronchially intubated and catheterised for drug administration and urine collection. After the first urine voiding (15 min.), blood is collected into anticoagulant to define the baseline LTB4 biosynthetic capacity of whole dog blood, and to determine the *in vitro* potency of this compound in dog blood. Compounds are dissolved in PEG 200/H_2O to a concentration of 0.3 mg/mL. In tubes #1-4, 10 μL of PEG 200 (vehicle) is added to serve as controls. Compounds are titrated from 0.0015 μM - 0.37 μM (final concentration). Compounds are added in a volume of 10 μL in ascending concentrations in duplicate (tubes #5-16). The highest drug concentration is also added to tube #17 as a drug blank. To each tube, 500 μL venous blood is added, followed by incubation for 15 minutes at room temperature, without shaking. Tubes #1 & 17, then receives 5 μL of autologous plasma containing 10% DMSO (blanks). 5 μL of autologous plasma containing 10% DMSO and 5 mM A23187 (final 50 μM) are

added to tubes #2 to 16 to stimulate LTB_4 synthesis. Samples are incubated for 30 min. at 37°C, and the reaction terminated by centrifugation. Aliquots of plasma is added to 4 volumes of MeOH, and centrifuged to precipitate proteins prior to analysis of LTB_4 content by RIA.

A bolus dose of compounds (0.1, 0.05 or 0.025 mg/kg in PEG200/H_2O) is then administered intravenously, followed by a continuous infusion (via a 21 gauge IV catheter) of the compounds (2.5, 0.8 or 0.25 μg/kg/min.). Urine is continuously collected for 1 hour intervals. Sample volumes are recorded, and urinary LTE_4 stabilised with 10N NaOH solution (10 μL/mL), prior to freezing (-70°C). Venous blood is similarly collected (into anticoagulant) contralateral to the IV at hourly intervals. All blood samples are immediately aliquoted (500 μL). To one aliquot, 5 μL of autologous plasma containing 10% DMSO is added as a blank. To other aliquots, 5 μL of autologous plasma containing 10% DMSO and 5 mM A23187 is added (final 50 μM) to stimulate LTB_4 synthesis as described above.

Aliquots (10 mL) of thawed urine are centrifuged (10,000 x g), and the supernatant adjusted to pH 5.4 with 100 μL glacial acetic acid. As a recovery standard, 3 nCi of [14,15,19,20-^{3}H]-LTC_4 (12 pg) is added. Samples are applied to a 3 μm particle C_{18} precolumn, and washed with 2 volumes of 0.1% NH_4OAc buffer pH 5.4. Peptide leukotrienes are then eluted onto a C_{18} analytical HPLC column, and separated with a 66% MeOH/34% 0.1% NH_4Ac pH 5.4 (v/v) mobile phase containing 1 mM EDTA. Fractions eluting with the retention time of synthetic LTC_4 (obtained from daily calibration with standards) are collected for estimation of [^{3}H]-LTC_4 recovery by scintillation counting. Prior experiments established that recoveries of [^{3}H]-LTC_4 and [^{3}H]-LTE_4 from dog urine after RP-HPLC are comparable (86.8 $\pm$ 1.9% and 83.1 $\pm$ 6.1% respectively). In some experiments synthetic LTE_4 (0.5 ng/mL) and/or 0.1 nCi [^{3}H]-LTE_4 (0.4 pg) are added to certain samples to identify the exact retention time of LTE_4. Fractions (0.75 min, 0.75 mL) eluting before, during and after the predicted retention time of synthetic LTE_4 (from daily calibration) are collected into sequential wells in a polypropylene microtitre plate, aliquots (200 μL) are removed

to identify the retention time of added [^{3}H]-LTE4), and the remainder frozen to -70°C and lyophilised in a vacuum centrifuge. Fractions are redissolved in 50 µL of 20 mM Na_2PO_4 pH 7.2 containing 0.9% NaCl, 0.02% sodium azide, 0.1 mM phenyl methyl sulphonyl fluoride and 1% gelatin and mixed with 2-3 nCi of [14,15,19,20-^{3}H]-LTE4 (5.2 - 7.8 pg) and an anti-LTC4 mouse monoclonal antibody (21% cross-reactivity with LTE4; final dilution 1/150,000) and incubated for 2 h at 21°C. Free ligand is precipitated by addition of dextran coated charcoal and centrifugation. An aliquot of the supernatant is removed and the concentration of LTE4 immunoactive material estimated by comparison of the unknown bound [^{3}H]-LTE4 against a standard curve derived by serial dilution of a synthetic LTE4 stock solution (4000 - 7.8 pg/tube). LTE4 concentration is calculated as the immunoreactive material (pg) in *n* co-eluting fractions - *n* x average background immunoreactive material (pg) in pre- and post-LTE4 fractions, corrected for [^{3}H]-LTC4 recovery, and the fraction volume removed for estimating the retention time of added [^{3}H]-LTE4. Urinary LTE4 excretion (ng/hour) is then calculated from the concentration and excretion volume, and related to values obtained during the first collection on a case by case basis. % inhibition of baseline LTE4 is calculated for the 5-6 and 6-7 h time points, and the mean value obtained for the treatment group. An ED_{50} is then calculated using these values and the infusion dose by non-linear regression analysis (4 parameter fit).

Aliquots (50 µL) of MeOH supernatants of plasma are similarly diluted into 50 µL of the above RIA buffer and mixed with 5-8 nCi of [5,6,8,9,11,12,14,15-^{3}H]-LTB4 (1.7 - 2.7 pg) and an anti-LTB4 sheep antiserum (final dilution 1/7500). LTB4 is quantified as above against a standard curve derived by serial dilution of a synthetic LTB4 stock solution (1000 - 1.95 pg/tube). LTB4 generation stimulated by 50 µM A23187 is derived by subtraction of the blank value (DMSO alone) and values are related to those obtained in the first (pre-treatment) sample. An ED_{50} is then calculated using the maximum values for *ex vivo* inhibition, and the infusion dose, by non-linear regression analysis. For the calculation of *in vitro* IC_{50} values, blank values for LTB4 production are subtracted from each subsequent value, and the %

inhibition calculated for each drug concentration (compared with PEG/H_2O). The IC_{50} is then calculated by non-linear regression analysis.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C;

(ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm. Hg) with a bath temperature of up to 60°C;

(iii) the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only;

(iv) melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;

(v) the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data;

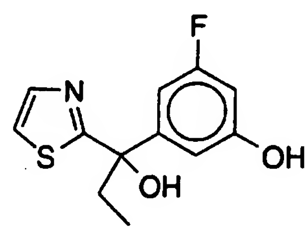
(vi) yields are given for illustration only;

(vii) when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; q. quartet; br. broad; etc.: in addition "Ar" signifies an aromatic signal;

(viii) chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliter(s)), µL (microliter(s)), g (gram(s)), mg (milligrams(s)), mol (mole(s)), mmol (millimole(s)), eq (equivalent(s)).

PREPARATION OF PHENOLS

PHENOL 1: 5-Fluoro-3-[1-hydroxy-1-(thiazol-2-yl)propyl]phenol



Step 1: 1-(Thiazol-2-yl) propanone

To a solution of thiazole (10 g, 0.12 mol) in dry THF (100 mL) at -78°C was added BuLi (50 mL, 2.47 M in hexane). The resulting reaction mixture was stirred 30 min. then ethyl propionate (18.8 mL, 0.16 mol) in THF was added and the cooling bath was removed. After 30 min. an aqueous solution of NH_4OAc (25%) was added and the THF evaporated. Ether was added and washed successively with H_2O, brine, dried over $MgSO_4$ and evaporated. The residue was distilled under vacuum to give 12.1 g (73%) of the title compound.

Step 2: 5-Fluoro-3-[1-hydroxy-1-(thiazol-2-yl)propyl](O-benzyl)-phenol

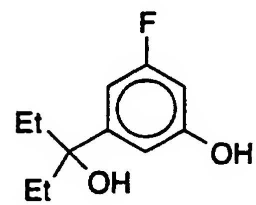
A solution of 3-benzyloxy-1-bromo-5-fluorobenzene (EP: 0385662, ICI, Pharma) (5.4 g, 19.4 mmol) in dry THF (30 mL) containing magnesium (941 mg, 38.7 mmol) was heated until the Grignard reagent was formed, then the reaction mixture was stirred at r.t. for 30 min. and transferred to a solution of 1-(thiazol-2-yl)-propanone in dry THF at 0°C. The reaction mixture was stirred for 30 min. then an aqueous solution of NH_4OAc (25%) was added and the THF evaporated. The residue was diluted with EtOAc and washed successively with H_2O, brine, dried over $MgSO_4$ and evaporated. The residue was purified by chromatography using hexane:EtOAc 9:1 to give 2.2 g, (50%) of the title product.

Step 3: 5-Fluoro-3-[1-hydroxy-1-(thiazol-2-yl)propyl]phenol

To a solution of 5-fluoro-3-[1-hydroxy-1-(thiazol-2-yl)-propyl](O-benzyl)phenol (200 mg, 0.58 mmol) in MeOH (9 mL) was added 10% Pd on charcoal (200 mg) and ammonium formate (180 mg, 2.9 mmol). The reaction mixture was refluxed for 2 h and then filtrated through a pad of celite and washed with EtOAc. After evaporation of the solvent, the residue was purified by chromatography on silica gel using a mixture of hexane:EtOAc 7:3 to give 116 mg (79%) of the title compound.

^1H NMR (400 MHz, $CDCl_3$); (0.89 (t, 3H); 2.32 (m, 2H); 3.44 (s, 1H); 5.59 (s, 1H); 6.42 (dd, 1H); 6.83 (m, 2H); 7.28 (d, 1H); 7.69 (d, 1H).

PHENOL 2: 5-Fluoro-3-(3-hydroxypent-3-yl)phenol



Step 1: 1-Bromo-3-(3,4-dimethoxybenzyloxy)-5-fluorobenzene

Sodium hydride (80% disp. in oil; 933 mg, 31.1 mmol) was added, all at once to 3,4-dimethoxybenzyl alcohol (3.48 g, 20.7 mmol) in DMF (40 mL) at 0°C and under Ar. After 5 min., the mixture was allowed to warm to r.t. After 1 h, 1-bromo-3,5-difluorobenzene (4 g, 20.7 mmol) in DMF (5 mL) was added dropwise at r.t. The resulting mixture was kept at this temperature for 16 h and slowly poured into H_2O (500 mL). It was extracted with EtOAc (3x) and the combined organics were washed with 25% NH_4OAc buffer (1x), H_2O (2x) and brine. The solution was dried ($MgSO_4$) and concentrated to give a pale yellow solid that was purified by column chromatography on silica gel (EtOAc:hexane, 10:90 - 15:85) to afford the title compound as a white solid (5.85 g, 83%).

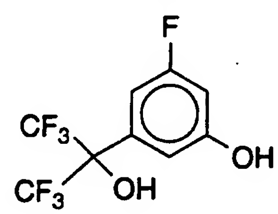
Step 2: 5-Fluoro-3-(3-hydroxypent-3-yl)[O-(3,4-dimethoxybenzyl)]phenol

To a solution of 1-bromo-3-(3,4-dimethoxybenzyloxy)-5-fluorobenzene (Step 1) (1.02 g) in THF (10 mL) at -78°C was added n-BuLi (1.5 mL of a 2.2 M solution) dropwise. After 30 min. 3-pentanone (0.33 mL) was added and after 30 min. the bath was removed and the mixture stirred for 10 min. The reaction mixture was quenched with NH_4OAc buffer and extracted with EtOAc. The organics were dried ($MgSO_4$) and concentrated. Chromatography of the residue (silica gel; hexane/EtOAc (3:1) provided the title compound as a colorless oil.

Step 3: 5-Fluoro-3-(3-hydroxypent-3-yl)phenol

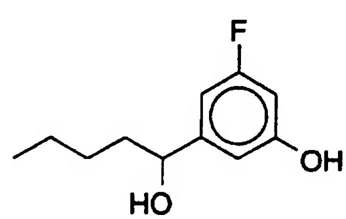
Following the procedure described for Phenol 1, Step 3, but substituting 5-fluoro-3-(3-hydroxypent-3-yl)[O-(3,4-dimethoxy-benzyl)]phenol from Step 2 for 5-fluoro-3-[1-hydroxy-1-(thiazol-2-yl)propyl](O-benzyl)phenol the title compound was obtained as a solid. ^{1}H NMR (300 MHz, Acetone-d_6); δ 0.72 (t, 6H); 1.78 (m, 4H); 3.61 (s, 1H); 6.41 (dd, 1H); 6.67 (dd, 1H); 6.76 (s, 1H); 8.50 (s, 1H).

<u>PHENOL 3</u>: <u>5-Fluoro-3-(hexafluoro-2-hydroxyprop-2-yl)phenol</u>



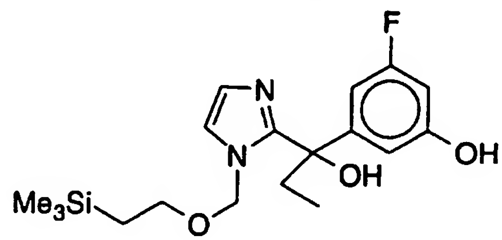
Following the procedure described for Phenol 2, Step 2, and Phenol 1, Step 3, but substituting hexafluoroacetone (Aldrich) for 3-pentanone, the title compound was obtained.
^{1}H NMR (300 MHz, Acetone-d_6); δ 6.75 (dd, 1H); 7.0 (d, 1H); 7.12 (s, 1H); 8.2 (s, 1H).

<u>PHENOL 4</u>: <u>5-Fluoro-3-(1-hydroxypentyl)phenol</u>



Following the procedure described for Phenol 2, Step 2 and for Phenol 1, Step 3, but substituting valeraldehyde for 3-pentanone, the title compound was obtained.
^{1}H NMR (300 MHz, Acetone-d_6); δ 0.9 (t, 3H); 1.2 - 1.4 (m, 4H); 1.6 - 1.7 (m, 2H); 4.6 (t, 1H); 6.45 (d, 1H); 6.6 (d, 1H); 6.7 (s, 1H); 7.95 (s, 1H).

PHENOL 5: 5-Fluoro-3-{1-hydroxy-1-[N-(2-trimethylsilylethoxymethyl)imidazol-2-yl]propyl}phenol



Step 1: 3-Benzyloxy-5-fluoropropiophenone

Following the procedure described for Phenol 2, Step 1, but substituting 3,5-difluoropropiophenone for 1-bromo-3,5-difluoro-benzene and benzyl alcohol for 3,4-dimethoxybenzyl alcohol as starting material, the title compound was obtained.

Step 2: 5-Fluoro-3-{1-hydroxy-1-[N-(2-trimethylsilylethoxymethyl)imidazol-2-yl]propyl}(O-benzyl)phenol

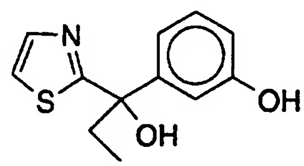
To a stirred solution of SEM-imidazole, (*Tet. Lett., 26,* 6273, **1985**) (252 mg, 1.27 mmol) in THF (5 mL) at -78°C under N_2 BuLi (857 µl, 1.4 M, 1.27 mmol) was added dropwise. The reaction mixture was stirred at -78°C for 20 min. and the ketone from Step 1 (274 mg, 1.06 mmol) was added dropwise. The reaction mixture was stirred at -78°C for 30 min. and then quenched with a 25% solution of NH_4OAc, concentrated and extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated to give an oil as the crude compound. The oil was purified by a flash silica column using hexane and EtOAc 9:1 as the eluant. The title compound was obtained as a transparent oil (188 mg, 39%) and used as such for the next step.

Step 3: 5-Fluoro-3-{1-hydroxy-1-[N-(2-trimethylsilylethoxymethyl)imidazol-2-yl]propyl}phenol

Following the procedure described for Phenol 1, Step 3 but substituting 5-fluoro 3-{1-hydroxy-1-[N-(2-trimethylsilylethoxymethyl)imidazol-2-yl]propyl}(O-benzyl)phenol from Step 2 for 5-fluoro-

3-[1-hydroxy-1-(thiazol-2-yl)propyl](O-benzyl)phenol, the title compound was obtained as an oil.
^{1}H NMR (400 MHz, $CDCl_3$); δ 0.03 (s, 9H); 0.7 - 0.8 (1t, 3H); 0.8 - 0.9 (1t, 2H); 1.9 - 2.25 (m, 1H); 2.30 - 2.40 (m, 1H); 3.12-3.22 (m, 1H); 3.30 - 3.40 (m, 1H); 4.08 (s, 1H); 4.95 (s, 2H); 6.04 (s, 1H); 6.45 - 6.52 (d, 1H); 6.65 (s, 1H); 6.99 (s, 1H); 6.72 - 7.0 (d, 1H).

PHENOL 6: 3-[1-Hydroxy-1-(thiazol-2-yl)propyl]phenol



Step 1: 3-Bromo-(O-tert-butyldimethylsilyl)phenol

To a solution of 3-bromophenol (50 g, 289 mmol) in 340 mL DMF was added Et_3N (35 g, 347 mmol) and tert-butyldimethylsilyl chloride (52 g, 347 mmol). The mixture was stirred for 0.5 h, and then diluted with Et_2O (2 L). The organic phase was washed with 5% aqueous HCl and brine, and dried over $MgSO_4$. Flash chromatography using hexane:EtOAc (95:5) gave 80.1 g (96%) of product.

Step 2: 3-[1-Hydroxy-1-(thiazol-2-yl)propyl]-(O-tert-butyldimethylsilyl)phenol

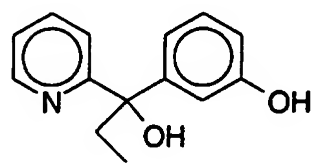
Following the procedure described for Phenol 2, Step 2, but substituting 3-bromo-(O-tert-butyldimethylsilyl)phenol from Step 1 for 1-bromo-3-(3,4-dimethoxybenzyloxy)-5-fluorobenzene and 1-(thiazol-2-yl)propanone from Phenol 1, Step 1, for 3-pentanone, the title compound was obtained.

Step 3: 3-[1-Hydroxy-1-(thiazol-2-yl)propyl]phenol

To a solution of compound from Step 2 (5.57 g, 15.96 mmol) in THF (40 mL) there was added n-Bu_4NF 1M in THF (18 mL); the mixture was stirred at r.t. for 30 min., then H_2O (10 mL) was added. The mixture was concentrated to a small volume, the residue extracted

with EtOAc, the extract washed twice with brine, dried and evaporated to a residue which was chromatographed on silica gel, eluting with a 1:1 mixture of EtOAc and hexane, to afford the title product as a white solid (2.59 g) m.p. 145-146°C.

PHENOL 7: 3-[1-Hydroxy-1-(pyridin-2-yl)propyl]phenol



Step 1: 3-Bromo(O-tert-butyldiphenylsilyl)phenol

Following the procedure described for Phenol 6, Step 1 but substituting tert-butyldiphenylsilyl chloride for tert-butyldimethylsilyl chloride the title compound was obtained.

Step 2: 3-(1-Hydroxypropyl)(O-tert-butyldiphenylsilyl)phenol

Following the procedure described for Phenol 2, Step 2 but substituting 3-bromo(O-tert-butyldiphenylsilyl)phenol from Step 1 for 1-bromo-3-(3,4-dimethoxybenzyloxy)-5-fluorobenzene and propionaldehyde for 3-pentanone, the title compound was obtained.

Step 3: 3-(tert-Butyldiphenylsilyloxy)propiophenone

To a solution of 3-(1-hydroxypropyl)(O-tert-butyldiphenylsilyl)phenol (11.7 g, 30 mmol) in CH_2Cl_2 (300 mL) at 0°C was added molecular sieves powder (8g, flame dried) followed by PCC (18 g, 84 mmol). The reaction mixture was stirred at r.t. for 1 h then poured on a silica gel column and eluted with Et_2O to give the title compound as an oil (10.8 g, 93%).

Step 4: 3-[1-Hydroxy-1-(pyridin-2-yl)propyl](O-tert-butyldi-phenylsilyl)phenol

n-BuLi (2.4 M in hexane, 674 µL, 1.62 mmol) was added dropwise (15 min.) to 2-bromopyridine (147 µL, 1.54 mmol) in THF (5

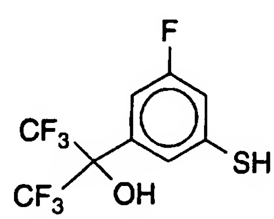
mL) at -78°C and under Ar. The solution was stirred for 40 min. at this temperature. The 3-(tert-butyldiphenylsilyloxy)propiophenone (499 mg, 1.28 mmol) from Step 3 in THF (2 mL) was then added dropwise (10 min.). The mixture was kept at -78°C for 30 min. and allowed to warm to 0°C. After 20 min. the reaction was quenched with a saturated NH_4Cl solution and extracted with EtOAc (3x). The combined organics were washed with 25% NH_4OAc buffer, H_2O, brine, dried ($MgSO_4$) and concentrated to give an off-white gum, that was purified by column chromatography on silica gel (EtOAc/hexane 1:9), affording the title compound as a colorless gum (563 mg, 94%).

Step 5: 3-[1-Hydroxy-1-(pyridin-2-yl)propyl]phenol

Following the procedure described for Phenol 6, Step 3 but substituting 3-[1-hydroxy-1-(pyridin-2-yl)propyl](O-tert-butyldiphenylsilyl)phenol from Step 4 for 3-[1-hydroxy-1-(thiazol-2-yl)propyl](O-tert-butyldimethylsilyl)phenol, the title compound was obtained.
^1H NMR (300 MHz, Acetone-d_6); δ 0.80 (t, 3H); 2.30 (q, 2H); 5.47 (s, 1H); 6.63 (m, 1H); 7.04 - 7.10 (m, 3H); 7.22 (m, 1H); 7.60 (d, 1H); 7.75 (m, 1H); 8.08 (s, 1H); 8.50 (d, 1H).

PREPARATION OF THIOPHENOLS

THIOPHENOL 1: 5-Fluoro-3-(hexafluoro-2-hydroxyprop-2-yl)-thiophenol



Step 1: 1,3-Difluoro-5-(hexafluoro-2-hydroxyprop-2-yl)benzene

To a solution of 1-bromo-3,5-difluorobenzene (4 g, 20.7 mmol) in dry THF (50 mL) containing magnesium (1 g, 41.5 mmol) was reflux until the Grignard reagent started to form. Then the reaction

mixture was stirred at r.t. for 30 min. Hexafluoroacetone was then bubbled in at 0°C until approximately 3.4 g was added. The mixture was stirred for 10 min. and quenched with 25% NH_4OAc. The resulting mixture was extracted with EtOAc and the combined organic phase was washed with H_2O, brine, dried over $MgSO_4$ and evaporated to give a residue which was chromatographed on silica gel, eluting with 9:1 mixture of hexane:EtOAc to afford the title compound (4.1 g, 71%) as a white solid.

<u>Step 2</u>: <u>5-Fluoro-3-(hexafluoro-2-hydroxyprop-2-yl)-1-(2-trimethylsilylethylthio)benzene</u>

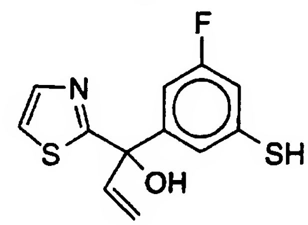
2-Trimethylsilylethane thiol (2.9 g, 21.9 mmol) was added dropwise to a suspension of NaH (1.8 g, 43.8 mmol) in dry DMF (60 mL) and stirred for 20 min. Then 1,3-difluoro-5-(hexafluoro-2-hydroxyprop-2-yl)benzene (Step 1) was added in dry DMF and the resulting reaction mixture was heated at 70°C for 16 h. The reaction mixture was then added carefully to H_2O and extracted with EtOAc. The combined organic phases were washed with brine, dried and evaporated to give a residue which was chromatographed on silica gel, eluting with 95:5 mixture of hexane:EtOAc to afford the title compound (3.2 g, 55%).

<u>Step 3</u>: <u>5-Fluoro-3-(hexafluoro-2-hydroxyprop-2-yl)thiophenol</u>

To a solution of 5-fluoro-3-(hexafluoro-2-hydroxyprop-2-yl)-1-(2-trimethylsilylethylthio)benzene (1 g, 2.54 mmol Step 2) in dry DMF (20 mL) was added tetrabutylammonium fluoride (1M in THF) (Aldrich) (6.4 mL, 6.4 mmol) and the reaction mixture was heated at 60°C for 30 min. The reaction mixture was then added to H_2O and extracted with EtOAc. The combined organic phase were washed with brine, dried and evaporated to give a residue which was chromatographed on silica gel eluting with 8:2 mixture of hexane:EtOAc to afford the title compound (330 mg, 44%).
^1H NMR (400 MHz, $CDCl_3$); δ 3.7 (s, 1H), 7.1 (d, 1H); 7.2 (d, 1H); 7.4 (s, 1H).

<u>THIOPHENOL 2</u>: 5-Fluoro-3-[3-hydroxy-3-(thiazol-2-yl)propen-

3-yl]thiophenol



Step 1: 3,5-Difluoro-α-(thiazol-2-yl)benzenemethanol

Following the procedure described for Thiophenol 1, Step 1, but substituting the 2-thiazole carboxaldehyde (*Synthesis*, *998*, **1987**) for hexafluoroacetone as starting material, the title compound was obtained as a liquid.

Step 2: (3,5-Difluorophenyl)(thiazol-2-yl)methanone

To a suspension of CrO_3 (1.1 g, 11 mmol) in CH_2Cl_2 at r.t. was added pyridine (1.8 mL, 22 mmol) and the resulting mixture was stirred for 20 min. The alcohol from Step 1 in CH_2Cl_2 was added and the resulting mixture was stirred for 16 h. Then Et_2O was added and the resulting mixture was filtered through silica gel and washed with Et_2O. After evaporation the residue was chromatographed on silica gel eluting with 7:3 mixture of hexane:EtOAc to give 1.66g (90%) of the title compound.

Step 3: 1,3-Difluoro-5-[3-hydroxy-3-(thiazol-2-yl)propen-3-yl]benzene

To a solution of (3,5-difluorophenyl)(thiazol-2-yl)-methanone (1 g, 4.4 mmol, Step 2) in dry THF (40 mL) was added at 0°C (4.4 mL, 4.4 mmol) of a 1.0 M THF solution of vinyl magnesium bromide (Aldrich). The reaction mixture was stirred for 30 min. and then transferred to a 1N aqueous HCl solution. The resulting mixture was extracted with EtOAc and the combined organic phase were washed with brine, dried over $MgSO_4$ and evaporated to give a residue which was chromatographed on silica gel eluting with 85:15 mixture of hexane: EtOAc to afford 635 mg (56%) of the title compound.

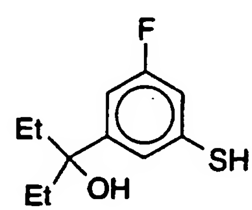
Step 4: 5-Fluoro-3-[3-hydroxy-3-(thiazol-2-yl)propen-3-yl]-1-(2-trimethylsilylethylthio)benzene

Following the procedure described for Thiophenol 1, Step 2, but substituting the 1,3-difluoro-5-[3-hydroxy-3-(thiazol-2-yl)-propen-3-yl]benzene from Step 3 for 1,3-difluoro-5-(hexafluoro-2-hydroxyprop-2-yl)benzene as starting material, the title compound was obtained as an oil.

Step 5: 5-Fluoro-3-[3-hydroxy-3-(thiazol-2-yl)propen-3-yl]-thiophenol

Following the procedure described for Thiophenol 1, Step 3, but substituting the 5-fluoro-3-[3-hydroxy-3-(thiazol-2-yl)propen-3-yl]-1-(2-trimethylsilylethylthio)benzene from Step 4 for 5-fluoro-3-(hexafluoro-2-hydroxyprop-2-yl)-1-(2-trimethylsilylethylthio)benzene as starting material, the title compound was obtained.

THIOPHENOL 3: 5-Fluoro-3-(3-hydroxypent-3-yl)thiophenol



Step 1: 3-Bromo-5-fluoro-1-(2-trimethylsilylethylthio)benzene

Following the procedure described for Thiophenol 1, Step 2, but substituting 1-bromo-3,5-difluorobenzene (Aldrich) for 1,3-difluoro-5-(hexafluoro-2-hydroxyprop-2-yl)benzene as starting material, the title compound was obtained.

Step 2: 5-Fluoro-3-(3-hydroxypent-3-yl)-1-(2-trimethylsilyl-ethylthio)benzene

Following the procedure described for Thiophenol 1, Step 1, but substituting the 3-bromo-5-fluoro-1-(2-trimethylsilylethylthio)-benzene from Step 1, for 1-bromo-3,5-difluorobenzene and 3-pentanone

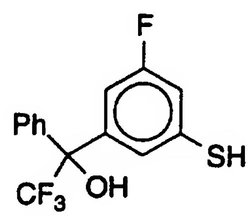
for hexafluoroacetone as starting material the title compound was obtained.

Step 3: 5-Fluoro-3-(3-hydroxypent-3-yl)thiophenol

Following the procedure described for Thiophenol 1, Step 3 but substituting the 5-fluoro-3-(3-hydroxypent-3-yl)-1-(2-trimethylsilylethylthio)benzene from Step 2 for 5-fluoro-3-(hexafluoro-2-hydroxyprop-2-yl)-1-(2-trimethylsilyethylthio)benzene as starting material, the title compound was obtained.

^{1}H NMR (300 MHz, Acetone-d_6); δ 0.71 (t, 6H); 1.79 (m, 4H); 3.71 (s, 1H); 4.49 (s, 1H); 6.92 - 6.98 (m, 2H); 7.19 (m, 1H).

THIOPHENOL 4: 5-Fluoro-3-(1-hydroxy-1-phenyl-2,2,2-trifluoroethyl)thiophenol



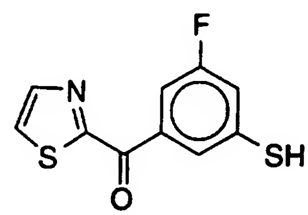
Step 1: 1,3-Difluoro-5-(1-phenyl-1-trimethylsilyloxy-2,2,2-trifluoroethyl)benzene

To a solution of 3,5-difluorobenzophenone (2.27 g, 10.4 mmol) in THF (5 mL) at 0°C was added trimethyl(trifluoromethyl)-silane (0.5 M in THF, 26 mL, 13.0 mmol) and a pinch of solid n-Bu_4NF. The mixture was stirred at r.t. for 17 h. Sat. aqueous NH_4Cl was added, the layers were separated and the organic phase was extracted with EtOAc (3x 20 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. Removal of the solvent and chromatography using hexane:EtOAc (95:5) gave 3.06 g of the title compound.

Step 2: 5-Fluoro-3-(1-hydroxy-1-phenyl-2,2,2-trifluoroethyl)-thiophenol

Following the procedure described for Thiophenol 1, Steps 2 and 3 but substituting the product from Step 1 for 1,3-difluoro-5-(hexafluoro-2-hydroxyprop-2-yl)benzene as starting material, the title compound was obtained.

THIOPHENOL 5: 5-Fluoro-3-(thiazol-2-ylcarbonyl)thiophenol



Step 1: (3-Methylthio-5-fluorophenyl)(thiazol-2-yl)methanone

To a solution of (3,5-difluorophenyl)(thiazol-2-yl)-methanone from Thiophenol 2, Step 2, (1.09 g, 4.84 mmol) in DMF (4.8 mL) was added sodium thiomethoxide (0.34 g, 4.84 mmol). The mixture was stirred for 4 h at r.t., then added to sat. aqueous NH_4Cl (100 mL) and extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent and chromatography using hexane: EtOAc (90:10) gave 0.80 g of the title product.

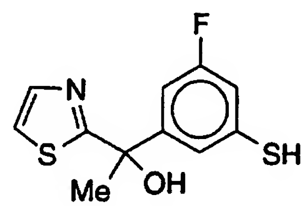
Step 2: (3-Methylsulfinyl-5-fluorophenyl)(thiazol-2-yl)methanone

To a solution of sulfide from Step 1 (0.76 g, 2.99 mmol) in MeOH (1.5 mL) and CH_2Cl_2 (6 mL) at 0°C was added the magnesium salt of monoperoxyphthalic acid (1.11 g, 1.80 mmol). The mixture was stirred at 0°C for 1.25 h and then sat. aqueous $NaHCO_3$ was added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and dried over anhydrous $MgSO_4$. Evaporation of the solvent and chromatography using toluene:EtOAc (25:75) gave 0.70 g of the title compound.

Step 3: 5-Fluoro-3-(thiazol-2-ylcarbonyl)thiophenol

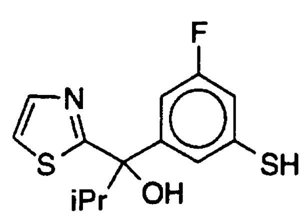
To a solution of the sulfoxide from Step 2 (0.35 g, 1.29 mmol) in dichloroethane (2.6 mL) was added TFAA (2.6 mL). The mixture was stirred at 80°C for 0.5 h, cooled and evaporated. The residue was dissolved in MeOH: Et3N (1:1, 5 mL). The solvent was evaporated and taken up again in MeOH/Et3N. After evaporation of the solvent and chromatography using hexane:EtOAc (70:30) 0.28 g of the title compound was obtained.
^{1}H NMR (300 MHz, Acetone-d$_6$); δ 7.5 (dd, 1H); 8.0 (d, 1H); 8.0 - 8.3 (2d, 3H).

THIOPHENOL 6: 5-Fluoro-3-[1-hydroxy-1-(thiazol-2-yl)ethyl]-thiophenol



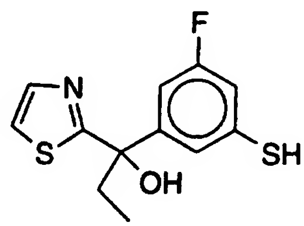
Following the procedure described for Thiophenol 2, Step 3 and Thiophenol 5, Steps 2 and 3 but substituting the ketone from Thiophenol 5, Step 1 for (3,5-difluorophenyl)(thiazol-2-yl)-methanone and methylmagnesium bromide (Aldrich) in THF for vinylmagnesium bromide as starting material, the title compound was obtained.

THIOPHENOL 7: 5-Fluoro-3-[1-hydroxy-2-methyl-1-(thiazol-2-yl)propyl]thiophenol



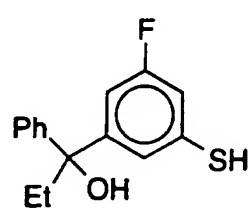
Following the procedure described for Thiophenol 2, Step 3 and Thiophenol 5, Steps 2 and 3 but substituting the ketone from Thiophenol 5, Step 1 for (3,5-difluorophenyl)(thiazol-2-yl)-methanone and isopropylmagnesium bromide (Aldrich) in THF for vinyl-magnesium bromide as starting material the title compound was obtained.

THIOPHENOL 8: 5-Fluoro-3-[1-hydroxy-1-(thiazol-2-yl)-propyl]-thiophenol



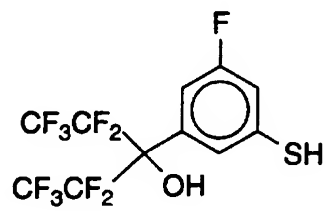
Following the procedure described for Thiophenol 2, Step 3 and thiophenol 5, Steps 2 and 3 but substituting the ketone from Thiophenol 5, Step 1 for (3,5-difluorophenyl)(thiazol-2-yl) methanone and ethylmagnesium bromide in THF (Aldrich) for vinylmagnesium bromide as starting material the title compound was obtained. Mass spec. 270 (MH+).

THIOPHENOL 9: 5-Fluoro-3-(1-hydroxy-1-phenylpropyl)thiophenol



Following the procedure described for Thiophenol 2, Step 3 and Thiophenol 1, Steps 2 and 3 but substituting 3,5-difluoropropiophenone (Lancaster) for (3,5-difluorophenyl)(thiazol-2-yl)methanone and phenylmagnesium bromide in THF (Aldrich) for vinylmagnesium bromide as starting material the title compound was obtained.

THIOPHENOL 10: 5-Fluoro-3-(decafluoro-3-hydroxypent-3-yl)thiophenol



Step 1: 3,5-Difluoro-1-(decafluoro-3-hydroxypent-3yl)benzene

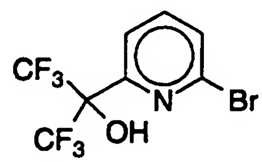
A three-necked flash was charged with 9.61 g (39.1 mmol) of pentafluoroethyl iodide at -78°C under a dry nitrogen atmosphere. 50 mL of Et2O was added followed by 1.38 g (7.82 mmol) of 3,5-difluorobenzoyl chloride (Aldrich). To the stirred solution was added 27.9 mL (39.1 mmol) of a 1.4 M solution of methyllithium/lithium bromide complex in diethyl ether. The reaction mixture was stirred for 0.5 h and then poured into a separating funnel containing 100 mL of a 5% aqueous hydrochloric acid solution and 50 mL of diethyl ether. After the layers were shaken and separated, the aqueous layer was further extracted with 25 mL of diethyl ether, and the combined extracts were dried over anhydrous magnesium sulfate. After filtration and solvent removal on a rotary evaporator, the product was distilled under reduced pressure to give 2.44 g (82%) of the tertiary alcohol, bp 70°-75°C (5 mm).

Step 2: 5-Fluoro-3-(decafluoro-3-hydroxypent-3-yl)thiophenol

Following the procedure described for Thiophenol 1, Step 2 and 3, but substituting 3,5-Difluoro-1-(decafluoro-3-hydroxypent-3-yl)benzene from Step 1 for 1,3-difluoro-5-(hexafluoro-2-hydroxyprop-2-yl)benzene, the title compound was obtained.

PREPARATION OF BROMOPYRIDINES

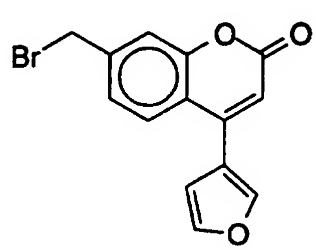
Bromopyridine 1: 2-Bromo-6-(hexafluoro-2-hydroxyprop-2-yl)pyridine



To a suspension of 2,6-dibromopyridine (2.37 g, 10 mmol) in THF (25 mL) at -70° there was added slowly n-BuLi, 1.4M, in hexane (7.9mL, 11 mmol). The resulting mixture was stirred in the cold until a solution was obtained (10 min). This solution was cannulated into a solution of hexafluoroacetone prepared by bubbling hexafluoroacetone into THF (10 mL) at -70° for 3 min. The resulting reaction mixture was stirred for 15 min., then quenched with an aqueous solution of NH_4Cl (8 mL). The suspension was allowed to warm to r.t. and was extracted with Et_2O. After drying and evaporation of the organic extract, the residue was chromatographed on silica gel with hexane:EtOAc, followed by bulb-to-bulb distillation to afford the title compound, m.p. 67-69° C.

PREPARATION OF COUMARINS

Coumarin 1: 7-Bromomethyl-4-(furan-3-yl)coumarin



Step 1: 3-Acetoxytoluene

To a solution of m-cresol (Aldrich) (80 g, 0.74 mol) in dry CH_2Cl_2 (300 mL) was added pyridine (71 mL, 0.89 mol) and at 0°C was

added dropwise acetyl chloride (58 mL, 0.81 mol). The reaction mixture was stirred for 1 h and then diluted with more CH_2Cl_2. The organic phase was washed successively with HCl 1N (3x), brine, dried over $MgSO_4$ and evaporated. The residue was distilled under vacuum to give 108 g (97%) of the title compound.

Step 2: 2-Hydroxy-4-methylacetophenone

To 50 g (0.33 mol) of 3-acetoxytoluene from Step 1 was added $AlCl_3$ (60 g, 0.45 mol) and the resulting mixture was heated at 165°C for 20 min., then cooled at 0°C and HCl 1N was carefully added followed by Et_2O. The aqueous phase was extracted 5x with Et_2O and the combined organic phase wash washed with brine, dried over $MgSO_4$ and evaporated. The residue was distilled under vacuum to give 42.2 (84%) of the title compound.

Step 3: 4-Hydroxy-7-methylcoumarin

A solution of 42 g (0.28 mol) of 2-hydroxy-4-methyl-acetophenone in benzene (150 mL) was added over 30 min. to a suspension of NaH (50% oil), 30 g, 0.63 mol) in 400 mL of benzene at reflux. Then, diethylcarbonate (67.8 mL, 0.56 mol) in benzene (500 mL) was added over 15 min. The reaction mixture was refluxed for 16 h and more NaH (13 g, 0.28 mol) was added followed by more diethylcarbonate (33 g, 0.28 mol). After another 6 h at reflux the reaction mixture was cooled to r.t. and HCl (2N) was added (1.5 L) to form a white precipitate. The solid was then filtered and added to a solution of NaOH (4N) (800 mL). The resulting basic solution was then extracted with Et_2O (2x 500 mL) and the basic solution acidified with HCl conc. to give a white solid which after filtration and dried gave 38.7 g (79%) of the title compound.

Step 4: 7-Methyl-4-trifluoromethanesulfonyloxycoumarin

To a solution of 4-hydroxy-7-methylcoumarin (10 g, 56.8 mmol) in CH_2Cl_2 (250 mL) was added Et_3N (9.5 mL, 68.2 mmol) and at 0°C was added trifluoromethanesulfonic anhydride (11.5 mL, 68.2 mmol). The reaction mixture was stirred for 16 h. Then more CH_2Cl_2

was added and the reaction mixture washed with HCl 1N (3x), brine dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography on silica gel using hexane:EtOAc 9:1 to give 10.6 g (61%) of the title compound.

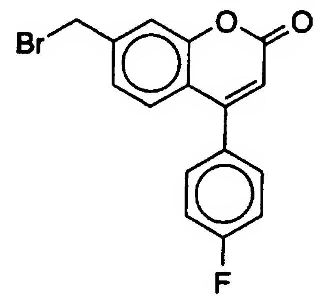
Step 5: 4-(Furan-3-yl)-7-methylcoumarin

To a solution of 3-bromofuran (1.9 g, 12.7 mmol) in dry Et_2O (30 mL) at -70°C was added BuLi in hexane (1.9 M, 6.7 mL, 12.7 mmol) and the resulting mixture was stirred for 20 min. Trimethyl borate (Aldrich) (1.4 mL, 12.7 mmol) was added dropwise and the mixture stirred for 20 min. A solution of the triflate from Step 4 in THF: H_2O (24 mL: 6 mL) containing $(Ph_3P)_4Pd$ (1.1 g, 0.97 mmol) was added and the reaction was heated to reflux for 16 h. The reaction mixture was cooled to r.t. and EtOAc was added and the organic phase washed with H_2O (3x), brine, dried over $MgSO_4$ and evaporated to give a white solid. A swish in EtOAc gave after filtration 1.8 g (82%) of the title compound.

Step 6: 7-Bromomethyl-4-(furan-3-yl)coumarin

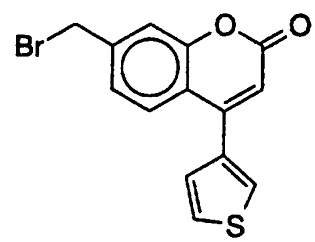
To a solution of 4-(furan-3-yl)-7-methylcoumarin (1.2 g, 5.3 mmol) in CCl_4 (40 mL) was added NBS (1 g, 5.8 mmol) followed by AIBN (87 mg, 0.53 mmol). The resulting mixture was refluxed for 4 h, then cooled to r.t. filtered and evaporated. Purification by chromatrography on silica gel gave 682 mg (42%) of the title compound. ^1H NMR (400 MHz, $CDCl_3$); 4.51 (s, 2H); 6.41 (s, 1H); 6.66 (s, 1H); 7.31 (d, 1H); 7.39 (s, 1H); 7.59 (s, 1H); 7.73 (d, 1H); 7.79 (s, 1H).

Coumarin 2: 7-Bromomethyl-4-(4-fluorophenyl)coumarin



Following the same procedure described for Coumarin 1, Steps 5 and 6 but substituting 4-fluoroiodobenzene for 3-bromofuran the title compound was obtained.

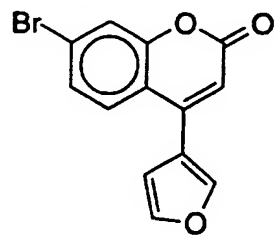
Coumarin 3: 7-Bromomethyl-4-(thien-3-yl)coumarin



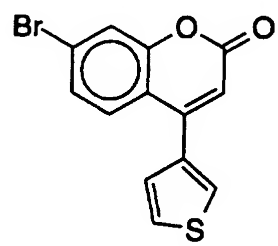
Following the same procedure described for Coumarin 1, Steps 5 and 6 but substituting 3-bromothiophene for 3-bromofuran the title compound was obtained.

Coumarins 4 to 10 were prepared following the procedure described for Coumarin 1, Steps 1 to 5 but substituting 3-bromophenol for m-cresol and substituting respectively in Step 5, 3-bromofuran, 3-bromothiophene, iodobenzene, 4-fluoroiodobenzene, 4-chloroiodobenzene, 2-trimethylsilyl-thiazole (Fluka), 2-chloro-3-bromothiophene for 3-bromofuran, the Coumarins 4 to 10 were obtained.

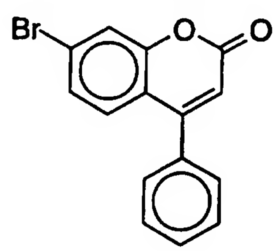
Coumarin 4: 7-Bromo-4-(furan-3-yl)coumarin



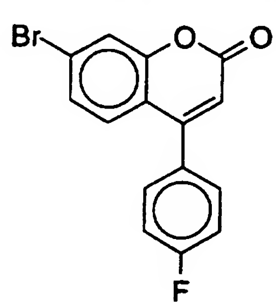
Coumarin 5: 7-Bromo-4-(thien-3-yl)coumarin



Coumarin 6: 7-Bromo-4-phenylcoumarin

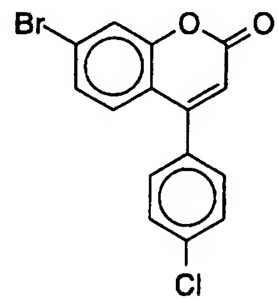


Coumarin 7: 7-Bromo-4-(4-fluorophenyl)coumarin

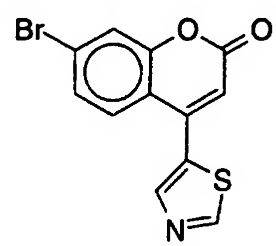


^{1}H NMR (400 MHz, $CDCl_3$); δ 6.35 (s, 1H); 7.20 (d, 2H); 7.30 (d, 1H); 7.35 (d, 1H); 7.41 (m, 2H); 7.6 (s, 1H).

Coumarin 8: 7-Bromo-4-(4-chlorophenyl)coumarin

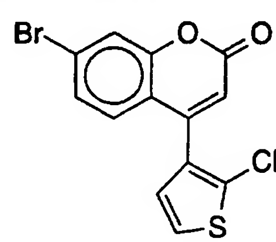


Coumarin 9: 7-Bromo-4-(thiazol-5-yl)coumarin



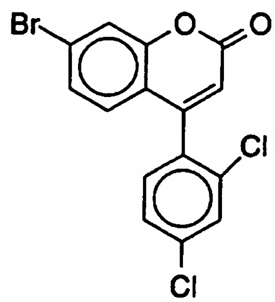
^{1}H NMR (400 MHz, $CDCl_3$); 6.52 (s, 1H); 7.52 - 7.55 (d, 1H); 7.58 - 7.62 (t, 2H); 8.14 (s, 1H); 9.0 (s, 1H).

Coumarin 10: 7-Bromo-4-(2-chlorothien-3-yl)coumarin



^{1}H NMR (400 MHz, Acetone-d_6); δ 6.5 (s, 1H); 7.4 (d, 1H); 7.5 - 7.6 (dd, 1H); 7.65 (d, 1H); 7.7 (d, 1H); 7.8 (d, 1H).

Coumarin 11: 7-Bromo-4-(2,4-dichlorophenyl)coumarin



Step 1: 7-Bromo-4-(trifluoromethanesulfonyloxy)coumarin

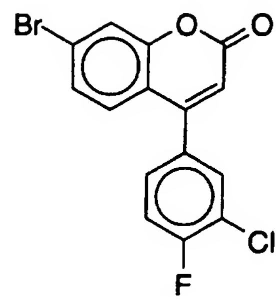
Following the procedure described for Coumarin 1, Steps 1 to 4 but substituting 3-bromophenol for m-cresol the title compound was obtained.

Step 2: 7-Bromo-4-(2,4-dichlorophenyl)coumarin

To a solution of the triflate from Step 1 (712 mg, 1.91 mmol) in 15 ml THF was added 2,4-dichlorophenyl boronic acid (400 mg, 2.10 mmol), $(Ph_3P)_4Pd$ (110 mg, 0.095 mmol) and aqueous Na_2CO_3 (1.91 mL, 3.82 mmol). The mixture was heated at 70°C for 2 h, cooled and partitioned between aqueous NH_4Cl and EtOAc (50 mL each). The layers were separated and the aqueous phase was extracted with EtOAc (3x25 mL). The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue chromatographed on silica gel (hexane: EtOAc 9:1) to give 480 mg (68%) of the title compound.

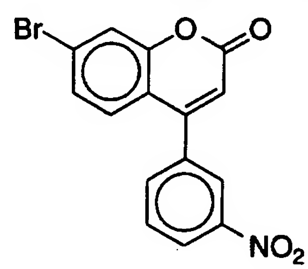
Coumarins 12 to 14 were prepared following the procedure described for Coumarin 11, Step 2 but substituting respectively 3-chloro-4-fluorophenyl boronic acid, 3-nitrophenyl boronic acid, and 3-trifluoromethoxyphenyl boronic acid for 2,4-dichlorophenyl boronic acid.

Coumarin 12: 7-Bromo-4-(3-chloro-4-fluorophenyl)coumarin



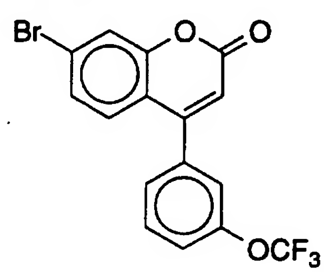
^1H NMR (400 MHz, Acetone-d_6); δ 6.5 (s, 1H); 7.4 - 7.5 (dd, 1H); 7.5 (dd, 1H); 7.5 - 7.6 (d, 1H); 7.6 (dq, 1H); 7.6 - 7.7 (d, 1H); 7.7 - 7.8 (dd, 1H).

Coumarin 13: 7-Bromo-4-(3-nitrophenyl)coumarin



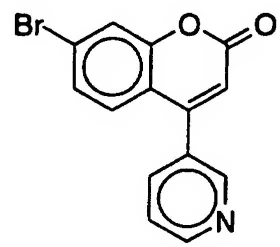
^1H NMR (400 MHz, Acetone-d_6); δ 7.4 (d, 1H); 7.5 (dd, 1H); 7.7 (d, 1H); 7.9 - 8.0 (d, 1H); 8.0 - 8.1 (m, 1H); 8.4 (dt, 2H).

Coumarin 14: 7-Bromo-4-(3-trifluoromethoxyphenyl)coumarin



^1H NMR (400 MHz, Acetone-d_6); 7.4 (d, 1H); 7.5 (dd, 1H); 7.5 - 7.6 (dt, 2H); 7.6 - 7.7 (dt, 1H); 7.7 (d, 1H); 7.7 (d, 1H); 7.7 - 7.8 (ddd, 1H).

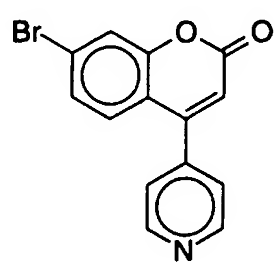
Coumarin 15: 7-Bromo-4-(pyridin-3-yl)coumarin



To a solution of 3-bromopyridine (0.10 mL) in THF (3 mL) stirred at -100°C was added a solution of n-BuLi in hexanes (1.4 M, 0.71 mL), after 10 min., the resulting yellow-green solution was treated with a solution of zinc chloride in THF (0.5 M, 2 mL) and the cold bath was removed. After another 10 min., triflate from Coumarin 11, Step 1 (376 mg) and $(Ph_3)_4Pd$ (46 mg) were added and the reaction mixture was stirred at r.t. for 1 h. Ethyl acetate was then added and the organic phase was washed successively with saturated aqueous $NaHCO_3$, H_2O and brine dried ($MgSO_4$), and evaporated. Flash chromatography of the residue (silica gel; hexane/EtOAc (1:3)) afforded the title compound as a yellow solid.

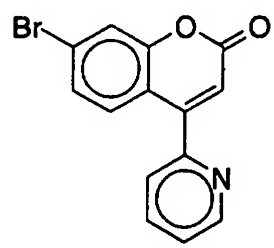
^{1}H NMR (400 MHz, $CDCl_3$); δ 6.40 (s, 1H); 7.25 (m, 1H); 7.35 (d, 1H); 7.50 (m, 1H); 7.60 (s, 1H); 7.75 (m, 1H); 8.70 (s, 1H), 8.80 (d, 1H).

Coumarin 16: 7-Bromo-4-(pyridin-4-yl)coumarin



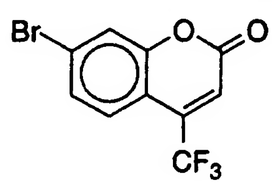
Following the procedure described for Coumarin 15, but substituting 4-bromopyridine for 3-bromopyridine, the title compound was obtained.
^1H NMR (400 MHz, $CDCl_3$); δ 6.36 (s, 1H); 7.18 - 7.26 (d, 1H); 7.30 - 7.40 (m, 4H); 7.58 - 7.70 (m, 2H); 8.80 (d, 2H).

Coumarin 17: 7-Bromo-4-(pyridin-2-yl)coumarin



Following the procedure described for Coumarin 15, but substituting 2-bromopyridine for 3-bromopyridine, the title compound was obtained.
^1H NMR ($CDCl_3$, 400 MHz); δ 6.50 (s, 1H); 7.35 (s, 1H); 7.45 (m, 1H); 7.55 (m, 2H); 7.65 (d, 1H); 7.90 (t, 1H); 8.80 (d, 1H).

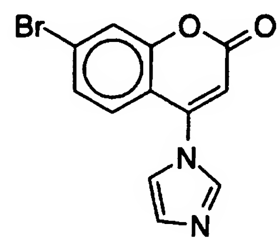
Coumarin 18: 7-Bromo-4-trifluoromethylcoumarin



To a solution of 48% HBr (4.5 g, 26.7 mmol) (3 mL) containing 7-amino-4-trifluoromethylcoumarin (Aldrich) (2.0 g, 8.8 mmol) at -10°C was added $NaNO_2$ (670 mg in 1 mL of H_2O) then Cu powder 35 mg was added. The reaction mixture was stirred at r.t. for 30 min., then heated to 100°C for 30 min. The reaction mixture was cooled to 0°C and H_2O (25 mL) was added. The mixture was extracted with EtOAc (400 mL) and the combined organic phase was washed with brine

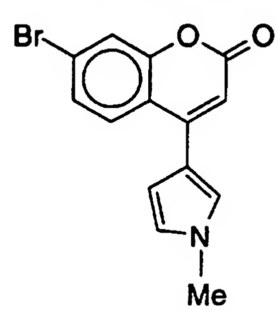
(200 mL) dried over $MgSO_4$ and evaporated. The crude solid was purified by chromatography on silica gel using hexane:EtOAc 8:2 as eluent, to give 1.5 g (58%) of the title compound as a white solid. ^1H NMR (400 MHz, Acetone-d_6); (7.0 (s, 1H); 7.6 - 7.8 (m, 3H).

Coumarin 19: 7-Bromo-4-(imidazol-1-yl)coumarin



The triflate from Coumarin 11, Step 1 (373 mg, 1 mmol) was mixed with imidazole (68 mg, 1 mmol) and K_2CO_3 (330 mg, 2.5 mmol) in n-methylpyrrolidone (4.0 mL) and the reaction was heated at 120°C for 30 min. The reaction mixture was diluted with EtOAc, washed with brine dried over $MgSO_4$, filtered and evaporated to give an oil which was purified on a silica gel column using hexane:EtOAc 9:1 as the eluent. The title compound was obtained as a white solid, (40 mg, 15%). ^1H NMR (400 MHz, $CDCl_3$); δ 6.48 (s, 1H); 7.24 (s, 1H); 7.30 (s, 1H); 7.36 - 7.40 (d, 1H); 7.46 - 7.48 (d, 1H); 7.6 (s, 1H); 7.8 (s, 1H).

Coumarin 20: 7-Bromo-4-(1-methylpyrrol-3-yl)coumarin



Step 1: 7-Bromo-4-(1-triisopropylsilyl-1H-pyrrol-3-yl)coumarin

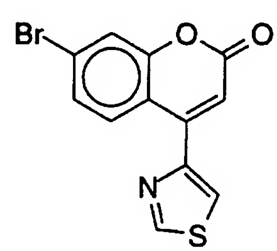
The triflate from Coumarin 11, Step 1 (298 mg, 0.8 mmol) was mixed with 1-(triisopropylsilyl)-3-(tributylstannyl)pyrrole (451 mg, 0.88 mmol) (*J. Org. Chem.*, *57*, 1653, **1992**) $(Ph_3P)_4Pd$ (37 mg, 0.032 mmol) and LiCl (101.7 mg, 2.4 mmol) in dioxane (2.0 mL) and the mixture was heated at reflux for 2.5 h. The reaction mixture was diluted in EtOAc, washed with brine, dried over $MgSO_4$, filtered and evaporated to give an oil which was purified on a silica column using toluene as the eluent. The title compound was obtained as an oil (100 mg) (28%).

Step 2: 7-Bromo-4-(1-methylpyrrol-3-yl)coumarin

To a solution of the silyl compound from Step 1 (42 mg, 0.094 mmol) in THF (1 mL) was added $n\text{-}Bu_4NF$ (1 M) in THF (94 µL, 0.094 mmol) and the reaction mixture was stirred at r.t. for 15 min. The mixture was diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and evaporated to give an oil (27 mg, 100%) which was dissolved in DMF (1 mL). Sodium hydride (97%, 2.8 mg, 0.11 mmol) was added at r.t. and stirred for 15 min. Then MeI (7 µL, 0.11 mmol) was added. The reaction mixture was stirred for 30 min. and then heated at 60°C for 30 min. The reaction mixture was then poured into H_2O and extracted with EtOAc. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated to give the title compound as an oil 29 mg (100%).

^1H NMR (400 MHz, $CDCl_3$); δ 3.75 (s, 3H); 6.3 (s, 1H); 6.4 (d, 1H); 6.72 (d, 1H); 6.95 (s, 1H); 7.2 (m, 2H); 7.92 (d, 1H).

Coumarin 21: 7-Bromo-4-(thiazol-4-yl)coumarin



Step 1: 7-Bromo-4-(1-ethoxyvinyl)coumarin

A mixture of triflate (from Coumarin 11, Step 1) (2.88 g), (1-ethoxyvinyl) tributyltin (3.06 g), $(Ph_3P)_4Pd$ (0.36 g) and LiCl (0.98 g) in dioxane (20 mL) was refluxed for 4 h. Ethyl acetate was then added and the organic phase was washed with H_2O and brine, dried ($MgSO_4$) and evaporated. Flash chromatrography of the residue (silica gel; hexane/EtOAc (9:1)) afforded the title compound as a yellow solid.

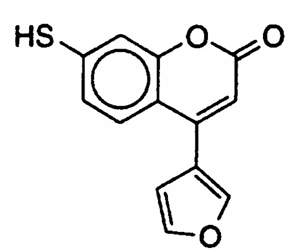
Step 2: 7-Bromo-4-(2-bromoacetyl)coumarin

To a solution of vinyl ether from Step 1 (1.02 g) in $CH_3CN:H_2O$ 4:1 (25 mL) were successively added NBS (0.82 g) and concentrated HBr (20 μL). After being stirred at r.t. for 4 h, the reaction mixture was treated with 5% aqueous $NaHSO_3$ (1 mL). Ethyl acetate was then added and the organic phase was washed with saturated aqueous $NaHCO_3$, H_2O and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue (silica gel; hexane/EtOAc (85:15)) afforded the title compound as a white solid.

Step 3: 7-Bromo-4-(thiazol-4-yl)coumarin

Freshly prepared thioformamide (*Helv. Chim. Acta, 31,* 2065, **1948**) (160 mg) was added to a solution of (α-bromoketone from Step 2 (200 mg) in THF (5 mL) and the reaction mixture was stirred at r.t. for 2 h. Ethyl acetate was then added and the organic phase was washed with saturated aqueous NH_4Cl, H_2O and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue (silica gel; hexane/EtOAc (65:35) afforded the title compound as a white solid. ^1H NMR (400 MHz, $CDCl_3$); δ 6.65 (s, 1H); 7.40 (d, 1H); 7.55 (s, 1H); 7.75 (s, 1H); 8.0 (d, 1H); 9.0 (s, 1H).

Coumarin 22: 7-Mercapto-4-(furan-3-yl)coumarin



Step 1: 7-(2-Trimethylsilylethylthio)-4-(furan-3-yl)coumarin

A mixture of 7-bromo-4-(furan-3-yl)coumarin (Coumarin 4) (1.5 g, 5.15 mmol), 2-(trimethylsilyl)ethanethiol (830 mg, 6.18 mmol), and K_2CO_3 (1.77 g, 12.9 mmol) in 1-methyl-2-pyrrolidinone (12 mL) was heated at 105°C for 4 h. After cooling, there was added saturated aqueous NH_4Cl (10 mL), then H_2O (50 mL) and the mixture was extracted twice with EtOAc. The organic extracts were washed 4 times with H_2O, dried over $MgSO_4$ and evaporated to a residue which was chromatographed on silica gel eluting with a 1:3 mixture of EtOAc and hexane, to afford the title compound (963 mg) as a tan solid.

Step 2: 7-Mercapto-4-(furan-3-yl)coumarin

The coumarin from Step 1 (963 mg) was dissolved in DMF (25 mL) and to this solution there was added n-Bu_4NF (1 M) in THF (8.4 mL). The mixture was stirred at r.t. for 2 h, poured onto 1N aqueous HCl (50 mL), diluted with H_2O (50mL) and filtered to afford the title compound (620 mg) as a tan solid. m.p.: 167-170°C.

EXAMPLE 1

3-{Furan-3-yl}-3-{4-[5-fluoro-3-(3-hydroxypent-3-yl)phenoxymethyl]-2-hydroxyphenyl}propenoic acid disodium salt

Step 1: 7-[5-Fluoro-3-(3-hydroxypent-3-yl)phenoxymethyl]-4-(furan-3-yl)coumarin

To a solution of Coumarin 1 (77 mg, 0.25 mmol), Phenol 2 (50 mg, 0.25 mmol) in dry DMF (5 mL) was added Cs_2CO_3 (99 mg, 0.3 mmol) and the resulting mixture was stirred at r.t. for 2 h. Then the reaction mixture was added to an aqueous solution of HCl (1N) and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated. Purification by flash chromatography using toluene: EtOAc (9:1) gave 95 mg (89%) of the title product.

^1H NMR (400 MHz, $CDCl_3$); δ 0.74 (t, J=7.5 Hz, 6H); 1.57 (s, 1H); 1.78 (m, 4H); 5.1 (s, 2H); 6.41 (s, 1H); 6.53 (dt, J=10.2 Hz, 1H); 6.66 (s, 1H); 6.67 (dt, 1H); 6.81 (s, 1H); 7.33 (m, 1H); 7.45 (s, 1H); 7.60 (s, 1H); 7.78 (m, 2H).

Step 2: 3-{Furan-3-yl}-3-{4-[5-fluoro-3-(3-hydroxypent-3-yl)phenoxymethyl]-2-hydroxyphenyl}propenoic acid disodium salt

A solution of the lactone from Step 1 in THF was treated with 2 equivalents of 1N NaOH and the mixture heated at reflux for 2 hrs. The solvent was removed *in vacuo* and the residue was lyophilized for 16 hrs to afford the title compound.
^1H NMR (400 MHz, DMSO-d_6); δ 0.65 (t, 6H); 1.65 (m, 4H); 4.75 (s, 2H); 6.0 (bs, 1H); 6.2 (s, 1H); 6.3 (bs, 1H); 6.55 (s, 1H); 6.65 (m, 3H); 6.8 (s, 1H); 6.95 (s, 1H); 7.45 (s, 1H).

EXAMPLE 2

3-{Furan-3-yl}-3-{4-[5-fluoro-3-(3-hydroxypent-3-yl)phenylthio)-2-hydroxyphenyl}propenoic acid disodium salt

Step 1: 7-[5-Fluoro-3-(3-hydroxypent-3-yl)phenylthio]-4-(furan-3-yl)coumarin

The Thiophenol 3 (81 mg, 0.378 mmol), the Coumarin 4 (143 mg, 0.491 mmol) and K_2CO_3 (130 mg, 0.945 mmol) were heated at 145°C in N-methyl-2-pyrrolidinone (2 mL) for 1 h. The mixture was allowed to cool to r.t. poured into H_2O (20 mL), and extracted with EtOAc (3x). The combined extracts were washed with 25% NH_4OAc buffer (1x), H_2O (2x), brine (1x), dried ($MgSO_4$) and concentrated. The brown residue obtained was purified by column chromatography on silica (EtOAc/hexane 1:4) to give a yellow foam (66 mg, 41%).
^1H NMR (300 MHz, Acetone-d_6); δ 0.74 (t, 6H); 1.84 (m, 4H); 3.87 (s, 1H); 6.39 (s, 1H); 6.90 (m, 1H); 7.12-7.20 (m, 3H); 7.30 (m, 1H); 7.47 (t, 1H); 7.80-7.84 (m, 2H); 8.16 (s, 1H).

Step 2: 3-{Furan-3-yl}-3-{4-[5-Fluoro-3-(3-hydroxypent-3-yl)-phenylthio}-2-hydroxyphenyl}propenoic acid disodium salt

Following the procedure described for Example 1, Step 2 but substituting compound from Step 1 for 7-[5-fluoro-3-(3-hydroxy-pent-3-yl)phenoxymethyl]-4-(furan-3-yl)coumarin, the title compound is obtained.

EXAMPLES 12-13

3-{4-Fluorophenyl}-3-{4-[5-Fluoro-3-(hexafluoro-2-hydroxyprop-2-yl)phenylsulfonyl]-2-hydroxyphenyl}propenoic acid disodium salt (Ex. 12) and 3-{4-Fluorophenyl}-3-{4-[5-Fluoro-3-(hexafluoro-2-hydroxy-prop-2-yl)phenylsulfinyl]-2-hydroxyphenyl}propenoic acid disodium salt (Ex. 13)

Step 1: 7-[5-Fluoro-3-(hexafluoro-2-hydroxyprop-2-yl)phenyl-sulfonyl]-4-(4-fluorophenyl) coumarin (Ex. 12) and 7-[5-fluoro-3-(hexafluoro-2-hydroxyprop-2-yl)phenylsulfinyl]-4-(4-fluorophenyl)coumarin (Ex. 13)

To a solution of the coumarin of Example 4 (100 mg, 0.19 mmol) in CH_2Cl_2 (5 mL) at 0°C was added mCPBA (65 mg) and the reaction mixture was stirred for 1 h. Then CH_2Cl_2 was added and washed with an aqueous solution of 10% NaOH, H_2O and brine, dried over $MgSO_4$ and evaporated. Purification by flash chromatography using toluene:EtOAc 85:15 gave 72 mg of the corresponding sulfone and 20 mg of the sulfoxide. Example 12; Mass spec.; 565 (MH^+); Example 13; Mass spec.; 549 (MH+).

EXAMPLE 12

Step 2: 3-{4-Fluorophenyl}-3-{4-[5-fluoro-3-(hexafluoro-2-hydroxyprop-2-yl)phenylsulfonyl]-2-hydroxy-phenyl}propenoic acid disodium salt

Following the procedure described for Example 1, Step 2 but substituting the sulfone from Step 1 for 7-[5-Fluoro-3-(3-hydroxy-pent-3-

yl)phenoxymethyl]-4-(furan-3-yl)coumarin, the title compound is obtained.

EXAMPLE 13

3-{4-Fluorophenyl}-3-{4-[5-fluoro-3-(hexafluoro-2-hydroxyprop-2-yl)phenylsulfinyl]-2-hydroxyphenyl}propenoic acid disodium salt

Following the procedure described for Example 1, Step 2 but substituting the sulfoxide from Step 1 for 7-[5-fluoro-3-(3-hydroxy-pent-3-yl)phenoxymethyl]-4-(furan-3-yl)coumarin, the title compound is obtained.

EXAMPLE 22

3-{4-Fluorophenyl}-3-{4-[5-fluoro-3-(1-hydroxy-1-(thiazol-2-yl)-2,2,2-trifluoroethyl)phenylthio]-2-hydroxyphenyl}propenoic acid disodium salt

Step 1: 7-[5-Fluoro-3-(thiazol-2-ylcarbonyl)phenylthio]-4-(4-fluorophenyl)coumarin

Following the procedure described for Example 2 but substituting Thiophenol 5 for Thiophenol 3 and Coumarin 7 for Coumarin 4 as starting material the title compound was obtained.

Step 2: 7-{5-Fluoro-3-[1-hydroxy-1-(thiazol-2-yl)-2,2,2-trifluoro-ethyl]phenylthio}-4-(4-fluorophenyl)coumarin

Following the procedure described for the preparation of Thiophenol 4, Step 1 but substituting the ketone from Step 1 for 3,5-difluorobenzophenone as starting material the title compound was obtained. m.p.: 72-73°C.

Step 3: 3-{4-Fluorophenyl}-3-{4-[5-fluoro-3-(1-hydroxy-1-(thiazol-2-yl)-2,2,2-trifluoroethyl)phenylthio]-2-hydroxyphenyl}propenoic acid disodium salt

Following the procedure described for Example 1, Step 2 but substituting compound from Step 2 for 7-[5-fluoro-3-(3-hydroxy-pent-3-yl)phenoxymethyl]-4-(furan-3-yl)coumarin, the title compound is obtained.

EXAMPLE 26

3-{Furan-3-yl}-3-{4-[5-fluoro-3-(1-hydroxy-1-(imidazol-2-yl)-propyl)phenoxymethyl]-2-hydroxyphenyl}propenoic acid disodium salt

Step 1: 7-(5-Fluoro-3-{1-hydroxy-1-[N-(2-trimethylsilyl-ethoxymethyl)imidazol-2-yl]propyl}phenoxymethyl)-4-(furan-3-yl)coumarin

Following the procedure described for Example 1, but substituting Phenol 5 for Phenol 2 as starting material, the title compound was obtained.

Step 2: 7-{5-Fluoro-3-[1-hydroxy-1-(imidazol-2-yl)propyl]-phenoxymethyl}-4-(furan-3-yl)coumarin

Under N_2 the compound from Step 1 (94 mg, 0.159 mmol) was dissolved in THF (2 mL). Tetrabutylammonium fluoride was added (795 µL, 0.795 mmol) and the reaction was stirred at 55°C for 1 h. Ethyl acetate was added and the organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated to give an oil which was purified by a flash silica column using EtOAc then 5% MeOH in CH_2Cl_2 as the eluent. The title compound was obtained: 12.8 mg (17%). Mass spec.: 461 (MH+).

Step 3: 3-{Furan-3-yl}-3-{4-[5-fluoro-3-(1-hydroxy-1-(imidazol-2-yl)propyl)phenoxymethyl]-2-hydroxyphenyl}propenoic acid disodium salt

Following the procedure described for Example 1, Step 2 but substituting compound from Step 2 for 7-[5-fluoro-3-(3-hydroxy-pent-3-yl)phenoxymethyl]-4-(furan-3-yl)coumarin, the title compound is obtained.

The following examples have been prepared according to the example referenced in each case, by coupling the identified components, followed by basic hydrolysis as described in Example 1, Step 2.

EXAMPLE 3

(Ex. 2; Thiophenol 1, Coumarin 4); ^{1}H NMR (400 MHz, DMSO-d_6); δ 6.15 (bs, 1H); 6.2 (s, 1H); 6.35 (bs, 1H); 6.58 (s, 1H); 6.7 (bs, 1H); 6.85 (d, 1H); 7.0 (s, 1H); 7.2 (bs, 1H); 7.55 (d, 2H).

EXAMPLE 4

(Ex. 2; Thiophenol 1, Coumarin 7); ^{1}H NMR (400 MHz, DMSO-d_6); δ 6.25 (s, 1H); 6.6 (d, 1H); 6.9 (d, 1H); 7.0 (2d, 2H); 7.2 (m, 3H); 7.6 (s, 1H).

EXAMPLE 5

(Ex. 2; Thiophenol 1, Coumarin 15); ^{1}H NMR (400 MHz, DMSO-d_6); δ 6.28 - 6.48 (m, 1H); 6.50 - 6.58 (t, 1H); 7.1 - 7.4 (m, 5H); 7.45 - 7.7 (m, 3H); 8.7 - 8.75 (t, 1H).

EXAMPLE 6

(Ex. 2; Thiophenol 1, Coumarin 9); ^{1}H NMR (400 MHz, DMSO-d_6); δ 6.4 (s, 1H); 6.42 - 6.5 (m, 1H); 6.55 - 6.62 (m, 1H); 6.85 - 6.98 (m, 2H); 7.4 - 7.5 (m, 2H); 7.6 (s, 1H); 8.88 (s, 1H).

EXAMPLE 7

(Ex. 2; Thiophenol 1, Coumarin 21); High resolution mass spec. (FAB: Glycerol); $C_{21}H_9NO_4S_2F_7Na_3H^+$ calcd 605.96326 found 605.96313

EXAMPLE 8

(Ex. 2; Thiophenol 1, Coumarin 16).

EXAMPLE 9

(Ex. 1; Phenol 3, Coumarin 2); Mass spec. FAB; 593 (MH)+.

EXAMPLE 10

(Ex. 2; Bromopyridine 1, Coumarin 22).

EXAMPLE 11

(Ex. 1; Phenol 4, Coumarin 2).

EXAMPLE 14

(Ex. 2; Thiophenol 1, Coumarin 8).

EXAMPLE 15

(Ex. 2; Thiophenol 1, Coumarin 11).

EXAMPLE 16

(Ex. 2: Bromopyridine 1, Coumarin 7); ^1H NMR (400 MHz, D_2O); δ 6.55 (s, 1H); 6.96 (m, 2H); 7.20 (m, 3H); 7.32 (m, 1H); 7.47 (m, 2H); 7.88 (m, 2H).

EXAMPLE 17

(Ex. 2; Thiophenol 1, Coumarin 17).

EXAMPLE 18

(Ex. 2; Thiophenol 1, Coumarin 20).

EXAMPLE 19

(Ex. 2; Thiophenol 1, Coumarin 6).

EXAMPLE 20

(Ex. 2; Thiophenol 1, Coumarin 19).

EXAMPLE 21

(Ex. 2; Thiophenol 4, Coumarin 4); Mass spec.: FAB; 575 $(M + 2Na-H)^+$.

EXAMPLE 23

(Ex. 2; Thiophenol 9, Coumarin 4); Mass spec.: FAB; 535 $(M + 2Na-H)^+$.

EXAMPLE 24

(Ex. 2; Thiophenol 6, Coumarin 4).

EXAMPLE 25

(Ex. 2; Thiophenol 7, Coumarin 4).

EXAMPLE 27

(Ex. 1; Phenol 7, Coumarin 1); ^1H NMR (400 MHz, DMSO-d_6); δ 0.7 (t, 3H); 2.22 (m, 1H); 2.35 (m, 1H); 4.75 (s, 2H); 6.2 (s, 1H); 6.35 (bs, 1H); 6.55 (s, 1H); 6.65 (bs, 1H); 6.75 (d, 1H); 6.95 (s, 1H); 7.05 (d, 1H); 7.15 (m, 3H); 7.5 (s, 1H); 7.65 (d, 1H); 7.7 (m, 1H); 8.48 (d, 1H).

EXAMPLE 28

(Ex. 1; Phenol 1, Coumarin 3); ^{1}H NMR (400 MHz, DMSO-d_6); δ 0.75 (t, 3H); 2.25 (m, 2H); 4.8 (s, 2H); 6.2 (bs, 1H); 6.33 (s, 1H); 6.4 (bs, 1H); 6.6 (bs, 1H); 6.7 (d, 1H); 6.83 (s, 1H); 6.9 (d, 1H); 7.05 (m, 2H); 7.3 (s, 1H); 7.55 (d, 1H); 7.75 (d, 1H).

EXAMPLE 29

(Ex. 1; Phenol 1, Coumarin 1); ^{1}H NMR (400 MHz, DMSO-d_6); δ 0.72 (t, 3H); 2.25 (m, 2H); 4.9 (s, 2H); 6.25 (s, 1H); 6.55 (m, 2H); 6.65 (bs, 1H); 6.75 (dd, 1H); 6.85 (bs, 1H); 6.9 (dd, 1H); 7.05 (m, 2H); 7.52 (m, 1H); 7.55 (d, 1H); 7.75 (d, 1H).

EXAMPLE 30

(Ex. 1; Phenol 1, Coumarin 2); ^{1}H NMR (400 MHz, DMSO-d_6); δ 0.72 (t, 3H); 2.25 (m, 2H); 4.92 (s, 2H); 6.2 (s, 1H); 6.55 (bs, 1H); 6.62 (d, 1H); 6.75 (m, 2H); 6.92 (d, 1H); 7.05 (m, 4H); 7.55 (d, 1H); 7.75 (d, 1H).

EXAMPLE 31

(Ex. 2; Thiophenol 8, Coumarin 4, Ex. 12-13, Step 1).

EXAMPLE 32

(Ex. 2; Thiophenol 8, Coumarin 10).

EXAMPLE 33

(Ex. 2; Thiophenol 8, Coumarin 5); Mass spec.: FAB; 558 $(M+2Na-H)^+$.

EXAMPLE 34

(Ex. 2; Thiophenol 8, Coumarin 6); Mass spec.: FAB; 552 $(M+2Na-H)^+$.

EXAMPLE 35

(Ex. 2; Thiophenol 8, Coumarin 4); Mass spec.: FAB; 542 $(M+2Na-H)^+$.

EXAMPLE 36

(Ex. 2; Thiophenol 8, Coumarin 7).

EXAMPLE 37

(Ex. 1; Phenol 6, Coumarin 1); Mass spec.: FAB; 522 $(M+2Na-H)^+$.

EXAMPLE 38

(Ex. 1; Phenol 6, Coumarin 3).

EXAMPLE 39

(Ex. 2; Thiophenol 1, Coumarin 13).

EXAMPLE 40

(Ex. 2; Thiophenol 1, Coumarin 12).

EXAMPLE 41

(Ex. 2; Thiophenol 10, Coumarin 7); Mass spec.: FAB; 717 $(M+3Na-2H)^+$.

EXAMPLE 42

(Ex. 2; Thiophenol 1, Coumarin 18).

EXAMPLE 43

(Ex. 2; Thiophenol 1, Coumarin 14).

EXAMPLE 44

3-{Furan-3-yl}-3-{4-[5-fluoro-3-(hexafluoro-2-methoxyprop-2-yl)phenylthio]-2-hydroxyphenyl} propenoic acid disodium salt

Step 1: 7-[5-Fluoro-3-(hexafluoro-2-methoxyprop-2-yl)phenylthio]-4-(furan-3-yl)coumarin

To a solution of the coumarin from Example 3 (1.02 g, 2.03 mmol) in 20 mL of THF at 0°C is added KH (466 mg, 4.06 mmol, 35% in oil). After 10 min. MeI (1.44 g, 10.1 mmol) is added dropwise. The solution is stirred for 30 min. at 0°C, then poured into saturated aqueous NH_4Cl. The aqueous layer is extracted with EtOAc (3 x 25 mL) and the combined organic layers are washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent and flash chromatography on silica gel gives the title compound.

Step 2: 3-{Furan-3-yl}-3-{4-[5-fluoro-3-(hexafluoro-2-methoxyprop-2-yl)phenylthio]-2-hydroxyphenyl}propenoic acid disodium salt

Following the procedure described for Example 1, Step 2 but substituting the compound from Step 1 for 7-[5-fluoro-3-(3-hydroxypent-3-yl)phenoxymethyl]-4-(furan-3-yl) coumarin, the title compound is obtained.

EXAMPLE 45

3-{4-Fluorophenyl}-3-{4-[5-fluoro-3-(hexafluoro-2-methoxyprop-2-yl)phenylthio]-2-hydroxyphenyl} propenoic acid disodium salt

Step 1: 7-[5-Fluoro-3-(hexafluoro-2-methoxyprop-2-yl)phenylthio]-4-(4-fluorophenyl)coumarin

To a solution of the coumarin from Example 4 (1.05 g, 2.03 mmol) in 20 mL of THF at 0°C is added KH (466 mg, 4.06 mmol, 35% in oil). After 10 min. MeI (1.44 g, 10.1 mmol) is added dropwise. The solution is stirred for 30 min. at 0°C, then poured into saturated aqueous NH4Cl. The aqueous layer is extracted with EtOAc (3 x 25 mL) and the combined organic layers are washed with brine and dried over anhydrous MgSO4. Evaporation of the solvent and flash chromatography on silica gel gives the title compound.

Step 2: 3-{4-Fluorophenyl}-3-{4-[5-fluoro-3-(hexafluoro-2-methoxyprop-2-yl)phenylthio]-2-hydroxyphenyl}propenoic acid disodium salt

Following the procedure described for Example 1, Step 2 but substituting the compound from Step 1 for 7-[5-fluoro-3-(3-hydroxypent-3-yl)phenoxymethyl]-4-(furan-3-yl) coumarin, the title compound is obtained.

WHAT IS CLAIMED IS:

1. A compound having the formula

$$R^1R^2C(OR^3)\text{-}Ar^1\text{-}X\text{-}Ar^2\text{-}C(Ar^3)\text{=}CHCO_2H$$

I

Ar^1	is a 6-membered aromatic ring, containing 0-3N, substituted with one or two of the same or different R^4 groups;
Ar^2	is Ph(OH), substituted with one or two of the same or different R^5 groups;
Ar^3 and Ar^4	are independently a 5-membered aromatic ring containing one O or S and 0-3 N; a 5-membered aromatic ring containing 1-4 N; or a 6-membered aromatic ring containing 0-3 N; wherein said aromatic ring is substituted with one or two of the same or different R^6 groups;
X	is OCH_2, CH_2O, O, S, S(O) or $S(O)_2$;
R^1	is H, lower alkyl, lower perfluoroalkyl or Ar^4;
R^2	is H, lower alkyl or lower perfluoroalkyl;
R^3	is H or lower alkyl;
R^4 and R^5	are H, lower alkyl, lower alkoxy, lower alkylthio, CN, CF_3, NO_2, CF_3O, or halogen;
R^6	is R^4, lower alkyl sulfinyl, lower alkylsulfonyl, or CO_2R^7;
R^7	is H, or lower alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein

Ar^1 is	Phe or Pye, each of which is substituted with one or two of the same or different R^4 groups;
Ar^3 is	Ph, Py, Fu, Th, Tz, Im, or Pyr, each of which is substituted with one or two of the same or different R^6 groups;
X is	OCH_2, CH_2O, S, S(O), or $S(O)_2$;
R^1 is	H, lower alkyl, lower perfluoroalkyl, Ph, Py, Im, Fu or Tz;

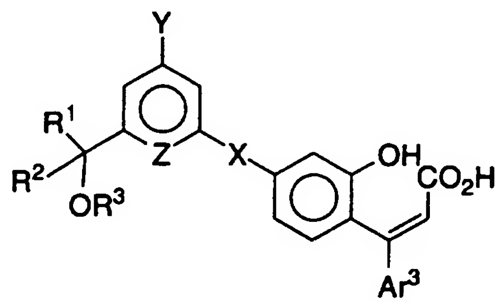
and the remaining substitutents are as defined in Claim 1.

3. A compound of Claim 1 wherein:

Ar^1 is	Phe or Pye each of which is unsubstituted or substituted with halogen;
Ar^3 is	Ph, Py, Fu, Th, Tz, Im, or Pyr each of which is substituted with one or two of the same or different R^6 groups;
X is	OCH_2, CH_2O, S, S(O) or $S(O)_2$;
R^1 is	H, lower alkyl, lower perfluoroalkyl, Ph, Py or Tz
R^6 is	R^4;

and the remaining substitutents are as defined in Claim 1.

4. A compound of Claim 1 having the formula Ia:



Ia

wherein

Ar^3	is Fu, Py, Tz, Im, N-lower alkyl-Pyr, Th optionally substituted with one halogen, Ph optionally substituted with one or two of the same or different halogen, or with one nitro or trifluoromethoxy;
R^1	is lower alkyl, lower perfluoroalkyl, Ph, Tz, Im, or Py;
R^2	is H, lower alkyl, or lower perfluoroalkyl;
R^3	is H or lower alkyl;
Y	is H or F;
X	is OCH_2, S, $S(O)_2$, S(O); and
Z	is CH or N.

5. A compound of Claim 4 wherein R^3 is H.

6. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1, 2, 3, 4 or 5 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

7. The pharmaceutical composition of Claim 6 additionally comprising an effective amount of a second active ingredient selected from the group consisting of non-steroidal anti-inflammatory drugs; peripheral analgesic agents; cyclooxygenase inhibitors; leukotriene antagonists; leukotriene biosynthesis inhibitors; H_1- or H_2-receptor antagonists; antihistaminic agents; prostaglandin antagonists; and ACE agonists.

8. A pharmaceutical composition according to Claim 7, wherein the second active ingredient is a non-steroidal anti-inflammatory drug.

9 A pharmaceutical composition of Claim 8, wherein the weight ratio of said compound of Claim 1 to said second active ingredient rangexs from about 1000:1 to 1:1000.

10. A method of preventing the synthesis, the action, or the release of SRS-A or leukotrienes in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 1.

11. The method of Claim 20 wherein the mammal is man.

12 A method of treating asthma in a mammal comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

13. A method of treating inflammatory diseases of the eye in a mammal which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

14. The method of Claim 12 wherein the mammal is man.

15. A pharmaceutically acceptable salt of a compound of formula (I) as defined in Claim 1, 2, 3, 4 or 5.

16. A compound of formula (I) as defined in Claim 1, 2, 3, 4 or 5, or a pharmaceutically acceptable salt thereof, for use in preventing synthesis, action or release of SRS-A or leukotrienes.

17. Use of a compound of formula (I) as defined in Claim 1, 2, 3, 4 or 5 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of asthma.

18. Use of a compound of formula (I) as defined in Claim 1, 2, 3, 4 or 5 or a pharmaceutically acceptable salt thereof, as a leukotriene biosynthesis inhibitor.

19. A leukotriene biosynthesis inhibitor pharmaceutical composition comprising an acceptable leukotriene biosynthesis inhibiting amount of a compound of formula (I), as defined in Claim 1, 2, 3, 4 or 5, in association with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Inte ...nal Application No
PCT/CA 95/00607

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D277/24 A61K31/425 C07D307/46 A61K31/34 C07C323/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US,A,5 360 815 (FORTIN) 1 November 1994 see claim 1 ---	1-18
A	EP,A,0 505 122 (ICI PHARMA) 23 September 1992 see claim 1 ---	1-18
A	EP,A,0 381 375 (ICI PLC) 8 August 1990 see claim 1 ---	1-18
A	EP,A,0 351 194 (ICI PHARMA) 17 January 1990 see claim 1 -----	1-18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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1

Date of the actual completion of the international search	Date of mailing of the international search report
11 January 1996	14.02.96

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Inte... ...nal Application No
PCT/CA 95/00607

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